

0.016 mmol): <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz): δH 9.94 (1H, d, J = 4.0 Hz), 8.35-8.37 (2H, m), 8.16 (2H, d, J = 8.0 Hz), 8.01 (1H, t, J = 7.4 Hz), 7.90 (1H, d, J = 10.0 Hz), 7.75 (1H, d, J = 8.0 Hz), 7.52 (2H, d, J = 8.0 Hz), 7.45 (1H, s), 7.40 (1H, d, J = 8.8 Hz), 3.96 (3H, s), 3.80 (2H, s), 3.42-3.45 (2H, m), 3.25 (2H, m), and 2.70-2.71 (2H, m); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R<sub>t</sub> 10.23 min. MS: MH<sup>+</sup> 610.2.

Example 514: N1-(4-{4-amino-1-[4-({[2-(dimethylamino)ethyl]amino)methyl]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of N1-(4-[4-amino-1-(4-formylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.080 g, 0.14 mmol), N,N-dimethylaminoethylamine (0.03 mL), and sodium triacetoxyborohydride (0.100 g, 0.472 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 24 h. 1N NaOH (1 mL) was added and the reaction mixture was concentrated, dissolved in DMF (2 mL), filtered through a syringe-tip Acrodisc filter, and purified by RP-HPLC (Rainin C18, 8 μm, 300 Å, 25 cm; 20-80% acetonitrile – 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 16.5-17.8 min was collected, concentrated, and lyophilized to afford N1-(4-{4-amino-1-[4-({[2-(dimethylamino)ethyl]amino)methyl]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide as a white solid (0.020 g, 0.032 mmol): <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz): δH 9.94 (1H, d, J = 4.4 Hz), 8.35-8.37 (2H, m), 8.15 (2H, d, J = 8.4 Hz), 8.01 (1H, t, J = 7.8 Hz), 7.90 (1H, d, J = 10.4 Hz), 7.75 (1H, d, J = 7.6 Hz), 7.50 (2H, d, J = 8.8 Hz), 7.45 (1H, s), 7.40 (1H, d, J = 8.0 Hz), 3.96 (3H, s), 3.77 (2H, s), 2.59 (2H, t, J = 6.6 Hz), 2.35 (2H, t, J = 6.6 Hz), and 2.12 (6H, s); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R<sub>t</sub> 10.85 min. MS: MH<sup>+</sup> 623.2.

Example 515: N1-(4-[4-amino-1-(2-hydroxyethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of 2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-ethanol (Intermediate 3) (0.120 g, 0.393 mmol), *N*1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide (0.190 g, 0.433 mmol), palladium tetrakis(triphenylphosphine) (0.045 g, 0.039 mmol), and sodium carbonate (0.100 g, 0.943 mmol) in DME (3.9 mL) and water (3.9 mL) was heated at 85 °C for 3 h. The reaction mixture was cooled to ambient temperature and the organic solvent was removed in vacuo. The precipitate was collected by filtration, rinsed with water (20 mL) and ether (20 mL), and dried in vacuo to afford *N*1-[4-[4-amino-1-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide as a brown solid (0.125 g, 0.254 mmol): <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz): δH 9.89 (1H, d, *J* = 4.0 Hz), 8.31 (1H, d, *J* = 8.0 Hz), 8.25 (1H, s), 7.99 (1H, t, *J* = 7.4 Hz), 7.89 (1H, d, *J* = 10.4 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 7.34 (1H, s), 7.31 (1H, d, *J* = 8.4 Hz), 4.89 (1H, s), 4.40 (2H, t, *J* = 5.6 Hz), 3.94 (3H, s), and 3.86 (2H, t, *J* = 5.6 Hz); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*<sub>t</sub> 9.85 min. MS: MH<sup>+</sup> 491.

Example 516: *N*2-[4-[4-amino-1-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A mixture of 2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-ethanol (Intermediate 3) (0.364 g, 1.19 mol), *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.485 g, 1.19 mmol), palladium tetrakis(triphenylphosphine) (0.138 g, 0.119 mmol), and sodium carbonate (0.303 g, 2.86 mmol) in DME (12 mL) and water (12 mL) was heated at 85 °C for 4 h then cooled to ambient temperature. The DME was removed in vacuo and the resulting precipitate was collected by filtration and rinsed with water (50 mL) and ether (50 mL) to afford *N*2-[4-[4-amino-1-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide as a tan solid (0.459 g, 1.00 mmol): <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz): δH 9.44 (1H, s), 8.26 (1H, s), 8.12 (1H, d, *J* = 8.0 Hz), 7.70 (1H, d, *J* = 8.0 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.29-7.41 (6H, m), 7.15 (1H, t, *J* = 7.4 Hz), 4.90 (1H, t, *J* = 5.8 Hz), 4.41 (2H, t, *J* = 5.8 Hz), 4.04 (3H, s), 3.96 (3H, s), and 3.86 (2H, q, *J* =

5.9 Hz); RP-HPLC (Hypersil C18, 5  $\mu$ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min).  $R_t$  10.52 min. MS: MH+ 458.2.

Example 517: *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide trimaleate

A mixture of 2-[4-amino-3-(3-methoxy-4-[[1-(methyl-1*H*-2-indolyl)carbonyl]amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.265 g, 0.495 mmol), *N*-methylpiperazine (0.065 mL, 0.58 mmol), and triethylamine (0.10 mL, 0.74 mmol) in DMF (5 mL) was heated at 70 °C for 20 h. The reaction mixture was cooled to ambient temperature and the solvent removed in vacuo. Water (25 mL) was added and the resulting precipitate was collected by filtration, washed with water (25 mL) and ether (50 mL), and dried in vacuo to afford a brown solid which was purified by silica gel column chromatography. The appropriate fractions were combined and concentrated to afford *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide as a beige solid (0.084 g, 0.16 mmol):  $^1\text{H}$  NMR ( $d_6$ -DMSO, 400 MHz):  $\delta$ H 9.44 (1H, s), 8.26 (1H, s), 8.11 (1H, d,  $J$  = 8.4 Hz), 7.70 (1H, d,  $J$  = 8.4 Hz), 7.29-7.35 (4H, m), 7.15 (1H, t,  $J$  = 7.4 Hz), 4.46 (2H, t,  $J$  = 6.8 Hz), 4.04 (3H, s), 3.96 (3H, s), 2.80 (2H, t,  $J$  = 6.6 Hz), 2.49-2.50 (2H, obscured by DMSO peak), 2.23-2.26 (4H, m), 2.12 (3H, s), and 0.97-0.99 (2H, m); RP-HPLC (Hypersil C18, 5  $\mu$ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min).  $R_t$  10.24. MS: MH+ 540.3.

To a mixture of *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.082 g, 0.15 mmol) in warm ethyl acetate (2 mL) was added a solution of maleic acid (0.053 g, 0.46 mmol) in warm ethyl acetate (1 mL). A precipitate formed immediately. The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration, washed with ethyl acetate (5 mL), and dried in vacuo to afford *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-

methyl-1*H*-2-indolecarboxamide trimaleate as a beige solid (0.090 g, 0.10 mmol):  
<sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz): δH 9.45 (1H, s), 8.27 (1H, s), 8.12 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 8.0 Hz), 7.59 (1H, d, J = 8.0 Hz), 7.29-7.36 (4H, m), 7.15 (1H, t, J = 7.4 Hz), 6.17 (6H, s), 4.50 (2H, t, J = 6.4 Hz), 4.04 (3H, s), 3.96 (3H, s), 3.10-3.20 (4H, m), 2.92-2.95 (4H, m), 2.74 (3H, s), and 2.32-2.37 (2H, m); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R<sub>t</sub> 10.48 min. MS: M+ 540.3.

Example 518: *N*2-{4-[4-amino-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide dimaleate

To a mixture of 2-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)carbonyl]amino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.200 g, 0.373 mmol), triethylamine (0.052 mL, 0.37 mmol), and sodium iodide (0.056 g, 0.37 mmol) in DMF (5 mL) was added morpholine (0.039 mL, 0.45 mmol). The reaction mixture was heated at 60 °C for 60 h. Morpholine (0.100 mL, 1.15 mmol) was added and the reaction mixture was heated at 80 °C for 30 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Water (5 mL) was added and the resulting precipitate was collected by filtration, washed with water (5 mL) and ether (10 mL), and dried in vacuo to afford a tan solid which was purified twice by silica gel chromatography (elution with 20% MeOH-CH<sub>2</sub>Cl<sub>2</sub>); the appropriate fractions were combined and concentrated to afford a beige solid which was triturated from ether and dried in vacuo to afford *N*2-{4-[4-amino-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide as a white solid (0.048 g, 0.054 mmol): <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz): δH 9.44 (1H, s), 8.26 (1H, s), 8.11 (1H, d, J = 8.0 Hz), 7.70 (1H, d, J = 7.6 Hz), 7.58 (1H, d, J = 7.6 Hz), 7.29-7.35 (4H, m), 7.15 (1H, t, J = 7.6 Hz), 4.48 (2H, t, J = 6.4 Hz), 4.04 (3H, s), 3.96 (3H, s), 3.50-3.53 (4H, m), 2.82 (2H, t, J = 6.2 Hz), and 2.47-2.51 (4H, m); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R<sub>t</sub> 10.02 min. MS: M+ 527.3.

To a mixture of *N*2-{4-[4-amino-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-



*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.048 g, 0.091 mmol) in warm ethyl acetate (2 mL) was added a solution of maleic acid (0.021 g, 0.18 mmol) in warm ethyl acetate (1 mL). A precipitate formed immediately. The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration, washed with ethyl acetate (5 mL), and dried in vacuo to afford *N*2-[4-[4-amino-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide dimaleate as a light brown solid (0.030 g, 0.039 mmol): <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz): δH 9.45 (1H, s), 8.31 (1H, s), 8.15 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.31-7.35 (4H, m), 7.16 (1H, t, *J* = 7.4 Hz), 6.17 (4H, s), 4.72-4.73 (2H, m), 4.04 (3H, s), 3.96 (3H, s), 3.72-3.79 (4H, m), and 3.10-3.30 (6H, obscured by water peak); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*<sub>t</sub> 11.08 min. MS: *M*+ 527.3.

15

Example 519: *N*2-[4-(4-amino-1-[2-[(2-hydroxyethyl)amino]ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide monomaleate

A mixture of 2-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)carbonyl]amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.080 g, 0.15 mmol), ethanolamine (0.05 mL, 0.82 mmol), triethylamine (0.021 mL, 0.15 mmol), and sodium iodide (0.021 g, 0.15 mmol) in DMF (2.5 mL) was heated at 70 °C for 15 h. The reaction mixture was cooled to ambient temperature and concentrated; water (5 mL) was added and the resulting precipitate was collected by filtration and rinsed with water (5 mL). The crude solid was purified by silica gel column chromatography (elution with 20% MeOH-CH<sub>2</sub>Cl<sub>2</sub>). The appropriate fractions were combined and the solvent removed in vacuo to afford *N*2-[4-(4-amino-1-[2-[(2-hydroxyethyl)amino]ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide as a white solid (0.009 g, 0.02 mmol). RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*<sub>t</sub> 9.39 min. MS: *M*+ 501.3.

- To a warm solution of *N*2-[4-(4-amino-1-{2-[(2-hydroxyethyl)amino]ethyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.009 g, 0.02 mmol) in ethyl acetate (2 mL) was added a solution of maleic acid (0.005 g, 0.04 mmol) in ethyl acetate (0.5 mL). The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration and dried in vacuo to afford *N*2-[4-(4-amino-1-{2-[(2-hydroxyethyl)amino]ethyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide monomaleate as a white solid (0.009 g, 0.014 mmol): <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz): δH 9.45 (1H, s), 8.69-8.74 (2H, bs), 8.31 (1H, s), 8.14 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.32-7.36 (4H, m), 7.15 (1H, t, *J* = 7.4 Hz), 6.07 (2H, s), 5.28 (1H, t, *J* = 4.2 Hz), 4.71 (2H, t, *J* = 5.8 Hz), 4.04 (3H, s), 3.96 (3H, s), 3.65-3.67 (2H, m), 3.50-3.60 (2H, m), and 3.10-3.20 (2H, m); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*<sub>t</sub> 9.97 min.
- MS: *M*+ 501.3.

Example 520: *N*2-[4-(4-amino-1-[2-(dimethylamino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide monomaleate

- A mixture of 2-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)carbonyl]amino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.080 g, 0.15 mmol), dimethylamine (2.0 M in THF, 0.07 mL, 0.15 mmol), triethylamine (0.021 mL, 0.15 mmol), and sodium iodide (0.021 g, 0.15 mmol) in DMF (2.5 mL) was heated in a resealable tube at 70 °C for 15 h. Additional dimethylamine solution (0.10 mL) was added and the reaction mixture was heated at 70 °C for 20 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Water (5 mL) was added and the resulting precipitate was collected by filtration and purified by silica gel column chromatography (elution with 20% MeOH:CH<sub>2</sub>Cl<sub>2</sub> to 10:30:60 Et<sub>3</sub>N:MeOH:CH<sub>2</sub>Cl<sub>2</sub>); the appropriate fractions were combined and concentrated to afford *N*2-[4-(4-amino-1-[2-(dimethylamino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide as a white solid (0.009 g,

0.02 mmol). RP-HPLC (Hypersil C18, 5  $\mu$ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min).  $R_t$  10.52. MS:  $M^+$  485.2.

- To a warm solution of *N*2-(4-{4-amino-1-[2-(dimethylamino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.009 g, 0.02 mmol) in ethyl acetate (2 mL) was added a solution of maleic acid (0.005 g, 0.04 mmol) in ethyl acetate (1 mL). The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration and dried in vacuo to afford *N*2-(4-{4-amino-1-[2-(dimethylamino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide monomaleate as a white solid (0.005 g, 0.008 mmol):  $^1\text{H}$  NMR ( $d_6$ -DMSO, 400 MHz):  $\delta$  9.46 (1H, s), 8.32 (1H, s), 8.15 (1H, d,  $J$  = 8.0 Hz), 7.71 (1H, d,  $J$  = 7.6 Hz), 7.59 (1H, d,  $J$  = 8.4 Hz), 7.32-7.35 (4H, m), 7.16 (1H, t,  $J$  = 7.4 Hz), 6.06 (2H, s), 4.75 (2H, t,  $J$  = 6.0 Hz), 4.04 (3H, s), 3.96 (3H, s), 3.65 (2H, t,  $J$  = 5.6 Hz), and 2.88 (6H, s); RP-HPLC (Hypersil C18, 5  $\mu$ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min).  $R_t$  10.08 min. MS:  $M^+$  485.2.

- Example S21: *N*2-(4-{4-amino-1-[2-(1*H*-1-imidazolyl)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide trimaleate

- A mixture of 2-[4-amino-3-(3-methoxy-4-[[1-(methyl-1*H*-2-indolyl)carbonyl]amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.080 g, 0.15 mmol), imidazole (0.011 g, 0.15 mmol), triethylamine (0.021 mL, 0.15 mmol), and sodium iodide (0.021 g, 0.15 mmol) in DMF (2.5 mL) was heated at 70 °C for 15 h. Imidazole (0.011 g, 0.15 mmol) was added and the reaction mixture was heated at 70 °C for 60 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Water (5 mL) was added and the resulting precipitate was collected by filtration to afford a beige solid which was taken up in hot ethyl acetate then allowed to slowly cool to ambient temperature. The filtrate was concentrated to afford *N*2-(4-{4-amino-1-[2-(1*H*-1-imidazolyl)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.034 g, 0.067 mmol): RP-

HPLC (Hypersil C18, 5  $\mu$ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min).  $R_f$  10.45 min. MS:  $M^+$  508.2.

- To a warm mixture of *N*2-(4-{4-amino-1-[2-(1*H*-1-imidazolyl)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.034 g, 0.067 mmol) in ethyl acetate (2 mL) was added a solution of maleic acid (0.016 g, 0.13 mmol) in ethyl acetate (1 mL); a white precipitate formed immediately. The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration and dried in vacuo to afford *N*2-(4-{4-amino-1-[2-(1*H*-1-imidazolyl)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide trimaleate as a yellow solid (0.011 g, 0.011 mmol):  $^1\text{H}$  NMR ( $d_6$ -DMSO, 400 MHz):  $\delta$  H 9.44 (1H, s), 8.90 (1H, s), 8.20 (1H, s), 8.12 (1H, d,  $J$  = 8.0 Hz), 7.71 (1H, d,  $J$  = 8.0 Hz), 7.58-7.63 (3H, m), 7.32-7.36 (2H, m), 7.24-7.26 (2H, m), 7.16 (1H, t,  $J$  = 7.6 Hz), 6.18 (6H, s), 4.85 (2H, t,  $J$  = 6.8 Hz), 4.71 (2H, t,  $J$  = 5.2 Hz), 4.04 (3H, s), and 4.00 (3H, s); RP-HPLC (Hypersil C18, 5  $\mu$ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min).  $R_f$  10.35 min. MS:  $M^+$  508.2.

Example 522: *N*1-{4-[4-Amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

- A solution of 2-fluoro-4-trifluoromethyl-1-benzenecarbonyl chloride (0.87 g, 3.83 mmol) in dichloromethane (5 mL) was added into a mixture of pyridine (15 mL) and 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-cyclohexanone (1.00 g, 2.56 mmol) in dichloromethane (5 mL) at 0°C over 5 minutes. The mixture was stirred at 0°C for 10 minutes and at ambient temperature overnight. The solvent was removed under reduced pressure. The residue was partitioned between water and dichloromethane. The dichloromethane layer was washed with saturated aqueous ammonium chloride twice and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography on silica using Isco system to provide *N*1-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.95 g, 1.76 mmol) as a white solid:  $^1\text{H}$  NMR

- (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.90 (dd, 1H), 8.30(d, 1H), 8.28 (s, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.34 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 5.27 (m, 1H), 3.94 (s, 3H), 2.70 (m, 2H), 2.47 (m, 4H), 2.17 (m, 2H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 $\mu$ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R<sub>t</sub> 9.23 min. MS: MH<sup>+</sup> 543.

- Example 523: *Cis-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide; and
- 10 Example 524: *Trans-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

- Morpholine (0.08 mL, 0.93 mmol) was added into a mixture of *N1*-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (Example 522) (0.42 g, 0.78 mmol) and acetic acid (0.11 mL, 1.86 mmol) in dichloroethane (25 mL). The mixture was stirred at ambient temperature for 10 minutes. Sodium triacetoxyborohydride (0.23 g, 1.09 mmol) was added and the mixture was stirred at ambient temperature overnight.
- 15 Water (6 mL) was added followed by sodium bicarbonate (0.38 g, 4.53 mmol). The mixture was stirred for 1 hour and the organic layer was separated. The aqueous layer was extracted with dichloromethane (20 mL). The combine organics were dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography on silica using Isco system to provide *cis-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.23 g, 0.37 mmol) and *trans-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.09 g, 0.14 mmol) as white solids.
- 25
- 30 Data for *cis-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.91 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H),

7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 4.83 (m, 1H), 3.94 (s, 3H), 3.62 (br, 4H), 1.57-2.55 (m, 10H); MS: MH<sup>+</sup> 614.

Data for trans-N1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1H-pyrazolo[3,4-

- 5 *d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.90 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 4.67 (m, 1H), 3.94 (s, 3H), 3.59 (br, 4H), 1.48-2.69 (m, 10H); MS: MH<sup>+</sup> 614.

- 10 Example 525: Cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate; and

Example 526: Trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate

- 15 A similar procedure to the preparation of cis-N1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide and trans-N1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide yielded cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate and trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate as white solids.

- 25 Data for cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.90 (dd, 1H), 8.30(d, 1H), 8.23 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 4.37 (m, 1H), 4.08 (q, 2H), 3.94 (s, 3H), 2.76 (m, 2H), 2.32 (m, 2H), 1.88 (m, 2H), 1.67 (m, 4H), 1.16 (t, 3H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min,

1 mL/min)  $R_t$  7.92 min. MS:  $MH^+$  644.

Data for trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate:  $^1H$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  9.89 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (d, 1H), 6.90 (br, 2H), 4.68 (m, 1H), 4.08 (q, 2H), 3.94 (s, 3H), 2.82 (m, 2H), 2.46 (m, 5H), 1.91-2.07 (m, 6H), 1.18 (t, 3H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 $\mu$ m, 100A, 250x4.6mm, 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)  $R_t$  7.69 min. MS:  $MH^+$  644.

Example 527: Cis-3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid

A mixture of cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate (Example 525) (0.23 g, 0.36 mmol), p-dioxane (15 mL), potassium hydroxide (0.10 g, 1.81 mmol) and water (1.5 mL) were heated at 80°C for 3 hours. The solvents were evaporated and the residue was purified by preparative HPLC to yield cis-3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid (0.11 g, 0.18 mmol) as a white solid:  $^1H$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  9.91 (dd, 1H), 8.31 (d, 1H), 8.25 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.35 (s, 1H), 7.32 (s, 1H), 6.89 (br, 2H), 4.79 (m, 1H), 3.95 (s, 3H), 2.46-3.00 (m, 7H), 2.29 (m, 2H), 1.91 (m, 2H), 1.80 (m, 2H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 $\mu$ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)  $R_t$  6.06 min. MS:  $MH^+$  616.

Example 528: Trans-3-({4-[4-amino-3-(3-methoxy-4-{[2-methoxy-4-trifluoromethylbenzoyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid

A mixture of trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-

- trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl]amino)propanoate (Example 526) (0.04 g, 0.06 mmol), p-dioxane (4 mL), potassium hydroxide (0.02 g, 0.31 mmol), a trace amount of methanol and water (0.4 mL) were heated at 80°C for 1 hour. The mixture was stirred at ambient temperature overnight and at 80°C for 4 hours. The solvents were evaporated and the residue was purified by preparative HPLC to yield trans-3-({4-[4-amino-3-(3-methoxy-4-([2-methoxy-4-trifluoromethylbenzoyl]amino)phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl]amino)propanoic acid (0.04 g, 0.06 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 10.72 (s, 1H), 8.61 (d, 1H), 8.28 (d, 1H), 8.24 (s, 1H), 7.61 (s, 1H), 7.53 (d, 1H), 7.33 (s, 1H), 7.29 (d, 1H), 4.72 (m, 1H), 4.20 (s, 3H), 4.05 (s, 3H), 1.44-3.61 (m, 13H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R<sub>t</sub> 6.36 min. MS: MH<sup>+</sup> 628.
- 15 Example 529: *N*1-[4-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide
- A. *N*1-[4-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide
- A mixture of 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.10 g, 0.19 mmol), *N*1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-trifluoromethylbenzamide (0.13 g, 0.29 mmol), tetrakis(triphenylphosphine)palladium(0) (0.01 g, 0.01 mmol) and sodium carbonate monohydrate (0.06 mg, 0.48 mmol) in water (2 mL) and ethylene glycol dimethyl ether (4 mL) was heated at 85°C overnight. The solvents were removed under reduced pressure. Water was added into the residue and the mixture was extracted with ethyl acetate three times. The combined organics were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield a brown solid which was purified by flash column chromatography on silica using Isco system to provide *N*1-[4-(4-amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.12 g, 0.17 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.89 (dd, 1H), 8.25 (d, 1H), 8.28 (s, 1H), 8.00 (t, 1H), 7.94 (s, 1H), 7.88



(d, 1H), 7.73 (d, 1H), 7.24 (m, 15H), 3.90 (s, 3H); MS: MH<sup>+</sup> 689.

B. *N*1-[4-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide

- 5 A mixture of *N*1-[4-(4-amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (2.10 g, 1.75 mmol), 6 N aqueous hydrochloric acid (10 mL), p-dioxane (10 mL) and ethanol (8 mL) was heated at 50°C for 6 hours. The mixture was filtered and the solid was washed with ethanol, dried in a vacuum oven over the weekend, and purified by flash column
- 10 chromatography on silica to provide *N*1-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.35 g, 0.78 mmol). The filtrate was concentrated and purified by flash column chromatography on silica and preparative HPLC to provide the same product *N*1-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-
- 15 trifluoromethylbenzamide (0.67 g, 1.51 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 13.58 (s, 1H), 9.90 (dd, 1H), 8.30(d, 1H), 8.23 (s, 1H), 8.05 (t, 1H), 7.90 (d, 1H), 7.75 (d, 1H), 7.36 (s, 1H), 7.24 (d, 1H), 3.94 (s, 3H); MS: MH<sup>+</sup> 447.

- Example 530: *N*1-[4-(4-Amino-1-tetrahydro-2*H*-4-pyran-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-
- 20 trifluoromethylbenzamide

- Diethyl azodicarboxylate (0.07 mL, 0.45 mmol) was added into a mixture of *N*1-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.10 g, 0.22 mmol), triphenylphosphine (0.12 g, 0.45
- 25 mmol) and tetrahydro-4*H*-pyran-4-ol (0.04 g, 0.34 mmol) in tetrahydrofuran (5 mL) and the mixture was stirred at ambient temperature overnight. Tetrahydro-4*H*-pyran-4-ol (0.01 g, 0.11 mmol), triphenylphosphine (0.04 g, 0.15 mmol) and diethyl azodicarboxylate (0.02 mL, 0.15 mmol) were added and the mixture was stirred at ambient temperature for 5 hours. The solvents were evaporated and the residue was
- 30 purified by preparative HPLC to yield *N*1-[4-(4-amino-1-tetrahydro-2*H*-4-pyran-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.03 g, 0.06 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.91 (dd, 1H), 8.30(d, 1H), 8.25 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75

(d, 1H), 7.34 (s, 1H), 7.31 (d, 1H), 6.90 (br, 2H), 4.95 (m, 1H), 4.02 (m, 2H), 3.95 (s, 3H), 3.56 (t, 2H), 2.22 (m, 2H), 1.89 (m, 2H); MS: MH<sup>+</sup> 531.

Example 531: *N*1-{4-[4-Amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

A. 4-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol

A mixture of tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol), 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.30 g, 1.14 mmol) and dimethyl sulfoxide (3 mL) was stirred at ambient temperature in the dark for 2 minutes and cooled to 0°C. A solution of 2,4*a*-dihydro-1*aH*-cyclopenta[*b*]oxirene (0.14 g, 1.72 mmol) in tetrahydrofuran (3 mL) was added into the mixture at 0°C and stirred at 0°C for 3 hours. The mixture was stirred at ambient temperature overnight and purified by preparative HPLC to yield 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol (0.24 g, 0.70 mmol) as a white solid; RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R<sub>t</sub> 4.23 min. MS: MH<sup>+</sup> 344.

B. *N*1-{4-[4-Amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

A mixture of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol (0.12 g, 0.35 mmol), *N*1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-trifluoromethylbenzamide (0.23 g, 0.53 mmol), tetrakis(triphenyl-phosphine)palladium(0) (0.02 g, 0.02 mmol) and sodium carbonate monohydrate (0.11 g, 0.88 mmol) was heated in a mixture of ethylene glycol dimethyl ether (6 mL) and water (3 mL) at 85°C for 6 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC to yield *N*1-{4-[4-amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-

pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.18 g, 0.34 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.89 (dd, 1H), 8.31(d, 1H), 8.26 (s, 1H), 8.00 (t, 1H), 7.88 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (d, 1H), 6.90 (br, 2H), 6.09 (d, 1H), 5.93 (d, 1H), 5.76 (m, 1H), 5.31 (m, 1H), 4.74 (m, 1H), 3.94 (s, 3H), 2.84 (m, 1H), 2.02 (m, 1H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R<sub>t</sub> 8.50 min. MS: MH<sup>+</sup> 529.

10 Example 532: *N*1-{4-[4-Amino-1-(3-hydroxycyclopentyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

A mixture of *N*1-{4-[4-amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.10 g, 0.19 mmol) and 10% palladium on carbon (0.03 g) in ethanol (10 mL) was stirred at ambient temperature under one atmosphere of hydrogen overnight. The mixture was filtered and the filtrate was purified by preparative HPLC to yield *N*1-{4-[4-amino-1-(3-hydroxycyclopentyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.07 g, 0.13 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.91 (dd, 1H), 8.31(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.34 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 5.17 (m, 1H), 4.97 (m, 1H), 4.22 (m, 1H), 3.94 (s, 3H), 1.79-2.41 (m, 6H); MS: MH<sup>+</sup> 531.

25 Example 533: 4-(4-Amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate

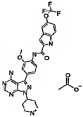
Oxalyl chloride (0.06 mL, 0.60 mmol) was added into a solution of indole-2-carboxylic acid (0.88 g, 0.546 mmol) in dichloromethane (5 mL) and tetrahydrofuran (5 mL) at 0°C. *N,N*-dimethylformamide (3 drops from 0.1 mL syringe) was added and the mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. The solvents and excess of reagents were evaporated under reduced pressure. The residue was taken into dichloromethane (2 mL) and the resulting

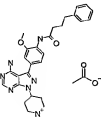
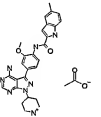
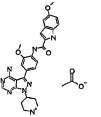
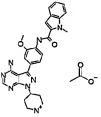
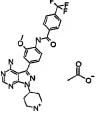
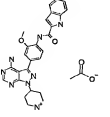
- solution (1.25 mL) was added into a solution of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.12 g, 0.27 mmol) and pyridine (0.4 mL) in dichloromethane (1 mL). The mixture was stirred at ambient temperature for 2 hours. Trifluoroacetic acid (1 mL) was added and the mixture was stirred at ambient temperature for 2 hours. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC to yield 4-(4-amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate (0.07 g, 0.14 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  11.85 (br, 1H), 9.45 (s, 1H), 8.24 (d, 1H), 8.12 (d, 1H), 7.68(d, 1H), 7.48 (d, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.30 (d, 1H), 7.24 (t, 1H), 7.09 (t, 1H), 4.77 (m, 1H), 3.97 (s, 3H), 3.11 (m, 2H), 2.68 (m, 2H), 2.09 (m, 2H), 1.89 (s, 3H), 1.84 (m, 2H); MS: MH<sup>+</sup> 483.

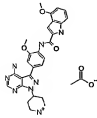
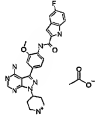
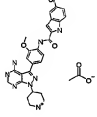
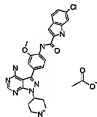
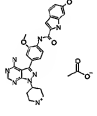
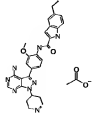
Example 534-549:

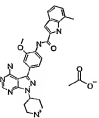
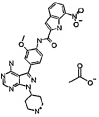
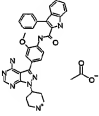
- Used the same protocol that was used to prepare 4-(4-amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate (Example 533), the following compounds were made.

20

Structure	MS: MH <sup>+</sup>	HPLC Rt (min) (Hypersil C18, 5 $\mu$ m, 100A, 250x4.6mm; 25 %- 100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)	Example No.
	567	6.97	534

	486	5.89	535
	497	6.28	536
	513	5.61	537
	497	6.39	538
	512	6.22	539
	483	5.73	540

	513	7.78	541
	501	8.23	542
	517	8.7	543
	517	8.73	544
	513	7.83	545
	511	9.07	546

	497	8.37	547
	528	7.9	548
	559	9.5	549

Example 550: 4-[4-Amino-3-(4-[[[(1-ethyl-1*H*-2-indolyl)carbonyl]amino]-3-methoxyphenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate

5

Sodium hydride, 60% suspension in mineral oil (0.006 g, 0.15 mmol) was added into the solution of *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1*H*-2-indolecarboxamide (0.08 g, 0.14 mmol) in *N,N*-dimethylformamide (1.0 mL) at 0°C. The mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. A solution of ethyl iodide (0.02 g, 0.14 mmol) in *N,N*-dimethylformamide (0.5 mL) was added in and the mixture was stirred at ambient temperature overnight. Ethyl iodide (0.01 g, 0.07 mmol) was added in and the mixture was stirred at ambient temperature overnight. Trifluoroacetic acid (3 mL) was added and the mixture was stirred at ambient temperature for 24 hours. The solvents and excess reagents were evaporated under reduced pressure and the residue was purified by preparative HPLC to yield 4-[4-amino-3-(4-[[[(1-ethyl-1*H*-2-indolyl)carbonyl]amino]-3-methoxyphenyl]-1*H*-

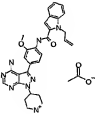
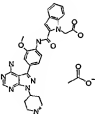
15

pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate (0.05 g, 0.09 mmol) as a white solid:  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.43 (s, 1H), 8.27 (s, 1H), 8.14 (d, 1H), 7.71(d, 1H), 7.61 (d, 1H), 7.34 (s, 2H), 7.31 (t, 2H), 7.15 (t, 1H), 4.96 (m, 1H), 4.62 (q, 2H), 3.96 (s, 3H), 3.00 (m, 2H), 2.28 (m, 2H), 2.03 (m, 2H), 1.91 (s, 3H),

5 1.33 (t, 3H); MS:  $\text{MH}^+$  511.

Example 551 and 552:

Used the same protocol that was used to prepare 4-[4-amino-3-(4-[(1-ethyl-1*H*-2-indolyl)carbonyl]amino)-3-methoxyphenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate (Example 550), the following compounds were made.

Structure	MS: MH+	HPLC Rt (min) (Hypersil C18, 5 $\mu\text{m}$ , 100A, 250x4.6mm; 25%- 100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)	Example No.
	523	9.12	551
	540	6.03	552

Example 553: 1-(1-methyl-3-piperidyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

15

A solution of racemic 3-iodo-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-



- d*]pyrimidin-4-amine (0.050 g, 0.00014 mol) in dimethoxyethane (2.5 mL) and water (5 mL) was treated with 4-phenoxyphenylboronic acid (0.033 g, 0.00015 mol), sodium carbonate (0.037 g, 0.00037 mol) and tetrakis (triphenylphosphine) palladium (0) (0.016 g, 0.000014 mol) at 80° C for 18 hours. The organic solvent was removed *in vacuo*, and the crude material was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give 1-(1-methyl-3-piperidyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.040 g, 0.00009 mol).
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.24 (s, 1H), 7.65 (d, 2H), 7.43 (t, 2H), 7.10- 7.22 (m, 5H), 4.74-4.84 (m, 1H), 2.94 (dd, 1H), 2.79 (d, 1H), 2.36 (t, 1H), 2.22 (s, 3H), 1.89 (s, 3H), 1.86-2.01 (m, 3H), 1.76-1.84 (m, 1H), 1.60-1.75 (m, 1H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.74 min.; MS: MH<sup>+</sup> 401.

Example 554: 1-[1-(2-methoxyethyl)-3-piperidyl]-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate BSF 4058532F.

- A solution of racemic 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.050 g, 0.00012 mol) in dimethoxyethane (2.5 mL) and water (5 mL) was treated with 4-phenoxyphenylboronic acid (0.029 g, 0.00014 mol), sodium carbonate (0.033 g, 0.00031 mol) and tetrakis(triphenylphosphine) palladium (0) (0.014 g, 0.00001 mol) at 80° C for 20 hours. The organic solvent was removed *in vacuo*, and the crude material was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give 1-[1-(2-methoxyethyl)-3-piperidyl]-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.038 g, 0.00007 mol).
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.24 (s, 1H), 7.65 (d, 2H), 7.43 (t, 2H), 7.09- 7.22 (m, 5H), 4.71-4.82 (m, 1H), 3.44 (t, 2H), 3.21 (s, 3H), 3.04 (dd, 1H), 2.91 (d, 1H), 2.47-2.60 (m, 3H), 1.94-2.09 (m, 3H), 1.89 (s, 3H), 1.75-1.84 (m, 1H), 1.57-1.74 (m,

1H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>f</sub> 14.26 min.; MS: MH<sup>+</sup> 445.

- 5 Example 555: *Trans* 1-{4-[4-amino-3-(3-chloro-4-[[4-(trifluoromethyl)benzoyl]amino}phenyl)-1H-pyrazolo[3,4-  
d]pyrimidin-1-yl]cyclohexyl}-4-methylhexahydropyrazinedium  
dimaleate

A. *Tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate

- 10 A solution of 4-bromo-2-chloroaniline (5.00 g, 0.0242 mol) in tetrahydrofuran (50 mL) was reacted with a 1.0 M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (53.2 mL, 0.0532 mol). The mixture was stirred 15 minutes at ambient temperature. Di-*tert*-butyl dicarbonate (6.34 g, 0.0290 mol) was added and the solution was stirred for 2 hours. The solvent was removed *in vacuo*, and the crude material was purified by flash column chromatography on silica  
15 using heptane /ethyl acetate (4:1). The solvent was removed *in vacuo* to give *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate as a white solid (4.214 g, 0.0137 mol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.75 (s, 1H), 7.71 (d, 1H), 7.54 (d, 1H), 7.50 (dd, 1H), 1.46 (s, 9H);  
20 TLC (heptane/ethylacetate 4:1) R<sub>f</sub> 0.54.

B. *Tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate

- A mixture of *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate (2.10 g, 0.00685 mol), diboron pinacol ester (2.09 g, 0.00822 mol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with  
25 dichloromethane (1:1) (0.17 g, 0.00021 mol) and potassium acetate (2.02 g, 0.02055 mol) in *N,N*-dimethylformamide (50 mL) was heated at 80°C under a nitrogen atmosphere for 6 hours. The solvent was removed *in vacuo*. The residue was  
30 triturated with heptane (70 mL) and the resulting solids were removed by filtration through a pad of Celite ® 521. The heptane was removed *in vacuo* to give *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate as a

grey solid (1.93 g, 0.00546 mol):  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.65 (s, 1H), 7.74 (d, 1H), 7.61 (d, 1H), 7.56 (dd, 1H), 1.47 (s, 9H), 1.29 (s, 12H).

C. *Trans tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate

A mixture of *trans* 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.20 g, 0.00498 mol), *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.93 g, 0.00548 mol), sodium carbonate (1.32 g, 0.01245 mol) in 1,2-dimethoxyethane (50 mL) and water (100 mL) was stirred rapidly and tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was added. The reaction mixture was stirred 6 hours at 80°C, after which time additional tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was added. The reaction mixture was stirred an additional 16 hours at 80°C. The solvents were removed *in vacuo* and the residue was partitioned between ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate (200 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 75 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The product was purified by flash column chromatography on silica using dichloromethane/methanol/ammonium hydroxide (90:10:0.5). The solvent was removed *in vacuo* to give *trans tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate as a white solid (1.993 g, 0.00368 mol):  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.76 (s, 1H), 8.23 (s, 1H), 7.80 (d, 1H), 7.68 (d, 1H), 7.57 (dd, 1H), 4.58-4.71 (m, 1H), 2.15 (s, 3H), 1.89-2.61 (m, 15H), 1.49 (s, 9H), 1.40-1.48 (m, 2H); TLC (dichloromethane/methanol = 90:10)  $R_f$  0.13, MS:  $M^+$  541.

D. *Trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

*Trans tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate (1.993 g, 0.00368 mol)

was added to a solution of 20% trifluoroacetic acid in dichloromethane. The mixture was stirred for 2 hours at ambient temperature. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (50 mL) and washed with a 1.0 M aqueous solution of sodium hydroxide (2 x 25 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to give *trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.564 g, 0.00355 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.45 (d, 1H), 7.31 (dd, 1H), 6.92 (d, 1H), 4.57-4.63 (m, 1H), 2.23-2.55 (m, 9H), 2.14 (s, 3H), 1.89-2.08 (m, 6H), 1.38-1.52 (m, 2H); TLC (dichloromethane/methanol = 90:10) R<sub>f</sub> 0.08; MS: MH<sup>+</sup> 441.

E. *Trans* N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)-4-(trifluoromethyl)benzamide dimaleate

To a mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in pyridine (5 mL) at -10° C 4-(trifluoromethyl)-1-benzenecarbonyl chloride (0.188 g, 0.00090 mol) was added dropwise, keeping the temperature below -5° C. The mixture was stirred at -10° C for 15 minutes, and then at ambient temperature for 18 hours. After addition of an 1N aqueous solution of sodium hydroxide (1.0 mL) the mixture was stirred one hour. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate (15 mL) and water (30 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (15 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the purified free base (0.032 g, 0.000052 mol). The free base was dissolved in absolute ethanol (4 mL) and heated to reflux. After addition of a solution of maleic acid (0.018 g, 0.000156mol) in absolute ethanol (1 mL) the solution was refluxed for further 15 minutes. The mixture was cooled to ambient

temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans* N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-chlorophenyl)-4-(trifluoromethyl)benzamide dimaleate as a white solid (0.020 g, 5 0.00002 mol): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.42 (s, 1H), 8.26 (s, 1H), 8.20 (d, 2H), 7.96 (d, 2H), 7.80-7.83 (m, 2H), 7.46 (dd, 1H), 6.80-7.20 (b, 2H), 6.13 (s, 4H), 4.61-4.73 (m, 1H), 2.52-2.64 (m, 4H), 2.23-2.46 (m, 5H), 2.16 (s, 3H), 1.90-2.10 (m, 6H), 1.42-1.56 (m, 2H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.97 10 min.; MS: MH<sup>+</sup> 613.

Example 556: *Trans* N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-chlorophenyl)-4-(trifluoromethoxy)benzamide dimaleate

15 To a mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in pyridine (5 mL) at -10° C 4-(trifluoromethoxy)-1-benzenecarbonyl chloride (0.203 g, 0.00091 mol) was added dropwise, keeping the temperature less than -5° C. The mixture was stirred at -10° C for 15 minutes and then at ambient temperature for 18 20 hours. After addition of an 1N aqueous solution of sodium hydroxide (1.0 mL) the mixture was stirred one hour. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate (15 mL) and water (30 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (15 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was removed 25 *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the purified free base (0.034 g, 0.000054 mol). The free base was dissolved in absolute ethanol (4 mL) and heated to 30 reflux. A solution of maleic acid (0.019 g, 0.000162 mol) in absolute ethanol (1 mL) was added and the solution was refluxed for 15 minutes. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal

amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans* N1-(4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-chlorophenyl)-4-(trifluoromethoxy)benzamide dimaleate as a white solid (0.020 g, 0.00002 mol):  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  10.29 (s, 1H), 8.26 (s, 1H), 8.14 (d, 2H), 7.78-7.87 (m, 2H), 7.68 (dd, 1H), 7.57 (d, 2H), 6.80-7.20 (b, 2H), 6.11 (s, 4H), 4.65-4.77 (m, 1H), 2.38-3.60 (m, 12H), 1.95-2.15 (m, 6H), 1.51-1.68 (m, 2H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  15.41 min.; MS:  $\text{MH}^+$  629.

10 Example 557: *Trans* 3-(3-chloro-4-[(5-methyl-2-furyl)methyl]amino)phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amineacetate

A mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.200 g, 0.00045 mol) in 1,2-dichloroethane (20 mL) was reacted with 5-methyl-2-furfural (0.052 g, 0.00048 mol), acetic acid (0.095 g, 0.00159 mol) and sodium triacetoxyborohydride (0.336 g, 0.00159 mol) at ambient temperature. An additional two equivalents of sodium triacetoxyborohydride (0.672 g, 0.00318 mol) were added in two 24 hour intervals. The solvents were removed *in vacuo* and the residue was partitioned between chloroform (25 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 25 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *trans* 3-(3-chloro-4-[(5-methyl-2-furyl)methyl]amino)phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine acetate as a white solid (0.129 g, 0.00022 mol):  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.20 (s, 1H), 7.51 (d, 1H), 7.39 (dd, 1H), 6.93 (d, 1H), 6.20 (d, 1H), 6.14 (t, 1H), 5.98 (d, 1H), 4.55-4.66 (m, 1H), 4.38 (d, 2H), 2.23 (s, 3H), 2.18-2.61 (m, 10 H), 2.14 (s, 3H), 1.91 (s, 3H), 1.87-2.09 (m, 5H), 1.37-1.53 (m, 2H); RP-HPLC (Delta Pak C18,

5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  14.48 min.;MS:  $MH^+$  535.

Example 558: *Trans* 3-{3-chloro-4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in 1,2-dichloroethane (20 mL) was reacted with 2-chloro-6-fluorobenzaldehyde (0.076 g, 0.00048 mol), acetic acid (0.095 g, 0.00159 mol) and sodium triacetoxyborohydride (0.336 g, 0.00159 mol) at ambient temperature. An additional three equivalents of sodium triacetoxyborohydride (1.008 g, 0.00477 mol) were added in three 24 hour intervals, after which time all the starting material had been consumed. The solvents were removed *in vacuo* and the residue was partitioned between chloroform (25 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 25 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 5 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give to give *trans* 3-{3-chloro-4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.074 g, 0.00011 mol):  $^1H$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.20 (s, 1H), 7.52 (d, 1H), 7.35-7.47 (m, 4H), 6.99 (d, 1H), 5.75 (t, 1H), 4.55-4.66 (m, 1H), 4.57 (d, 2H), 2.25-2.61 (m, 11 H), 2.16 (s, 3H), 1.91 (s, 3H), 1.87-2.09 (m, 4H), 1.37-1.53 (m, 2H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  15.97 min.;MS:  $MH^+$  583.

Example 559: *Trans* N1-(4-{4-amino-1-[1-(1*H*-2-imidazo[*l*]carbonyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-

## phenyl-1-cyclopropanecarboxamide maleate

- A mixture of *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-phenyl-1-cyclopropanecarboxamide (0.200 g, 0.00041 mol) in toluene (10 mL) was reacted with 5*H*,10*H*-diimidazo[1,5-*α*:1,5-*d*]pyrazine-5,10-dione (0.040 g, 0.00021 mol) at reflux for 18 hours. An additional equivalent of 5*H*,10*H*-diimidazo[1,5-*α*:1,5-*d*]pyrazine-5,10-dione was added and the mixture was refluxed an additional 6 hours. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the free base (0.103 g, 0.00017 mol). The free base was dissolved in absolute ethanol (10 mL) and heated to reflux. After addition of a solution of maleic acid (0.030 g, 0.00034 mol) in absolute ethanol (1 mL) the solution was refluxed for 15 minutes, after which time a precipitate formed. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans* *N*1-(4-{4-amino-1-[1-(1*H*-2-imidazolylcarbonyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide maleate as a white solid (0.055 g, 0.00008 mol):
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.63 (s, 1H), 8.26 (s, 1H), 8.22 (d, 1H), 8.00 (b, 1H), 7.74 (b, 1H), 7.43-7.48 (m, 1H), 7.16-7.33(m, 7H), 6.21 (s, 2H), 4.97-5.13 (m, 1H), 2.91-3.47 (m, 4H), 2.53-2.65 (m, 1H), 2.30-2.45 (m, 1H), 2.07-2.26 (m, 2H), 1.95-2.07 (m, 2H), 1.45-1.50 (m, 1H), 1.28-1.32 (m, 1H); RP-HPLC ( Delta Pak C18, 5μm, 300Å, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.17 min.; MS: MH<sup>+</sup> 578.

Example 560: *Cis* *N*1-(4-[4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide acetate

- A. *Cis* *N*1-(4-[4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide



A mixture of *cis* N1-[4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenylcyclopropane-1-carboxamide (0.605 g, 0.0012 mol), lithium perchlorate (0.189 g, 0.0018 mol) and potassium cyanide (0.116 g, 0.0018 mol) in acetonitrile (60 mL) was heated at 80°C for two days. Cooled to ambient temperature, diluted with water (30 mL) and extracted with diethyl ether (3x 30 mL). The combined organic phases were dried over magnesium sulfate. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica using dichloromethane/methanol (95:5). The solvent was removed *in vacuo* to give *cis* N1-(4-[4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide as a white solid (0.602 g, 0.0011 mol): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.64 (s, 1H), 8.23 (t, 2H), 7.31 (t, 2H), 7.25 (s, 1H), 7.17- (m, 4H), 4.61-4.62 (m, 1H), 3.91 (s, 1H), 2.66 (s, 2H), 2.55-2.62 (m, 1H), 2.31-2.45 (m, 3H), 1.58-1.89 (m, 6H), 1.45-1.53 (m, 1H), 1.28-1.38 (m, 1H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 15.21 min.; MS: MH<sup>+</sup> 538.

B. *Cis* N1-(4-[4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide acetate

To a solution of *cis* N1-(4-[4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropane-carboxamide (0.200 g, 0.00037 mol) in methanol (20 mL) and ammonium hydroxide (1 mL) Raney nickel (0.5 mL) was added. The mixture was stirred 18 hours under a hydrogen atmosphere (1 atm). The reaction mixture was filtered through celite and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *Cis* N1-(4-[4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-

- cyclopropanecarboxamide acetate as a white solid (0.045 g, 0.00083 mol):  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  9.64 (s, 1H), 8.23 (d, 1H), 8.22-8.24 (m, 1H), 7.17-7.33 (m, 7H), 4.65-4.67 (m, 1H), 3.91 (s, 3H), 2.84-2.91 (m, 1H), 2.53-2.55 (m, 1H), 2.33-2.40 (m, 4H), 1.85 (s, 3H), 1.35-1.80 (m, 9H), 1.30-1.33 (m, 1H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  13.29 min.; MS:  $\text{MH}^+$  444

- Example 561: *Cis* N1-(4-{4-amino-1-[4-(2-amino-2-oxoethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide
- To a well-stirred solution of *cis* N1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide (0.200 g, 0.00037 mol) in dimethylsulfoxide (4 mL) potassium carbonate (0.216 g, 0.00156 mol) was added at ambient temperature. A 30% aqueous solution of hydrogen peroxide (0.6 mL) was added dropwise, keeping the temperature constant. The mixture was stirred at ambient temperature for 32 hours. Water (20 mL) was added to the mixture, and the precipitate which formed was filtered. The precipitate was washed with water and dried *in vacuo*. The solid was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *cis* N1-(4-{4-amino-1-[4-(2-amino-2-oxoethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide as a white solid (0.117 g, 0.00021 mol):  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  9.64 (s, 1H), 8.23 (d, 1H), 8.22 (s, 1H), 7.43-7.48 (m, 1H), 7.15-7.35 (m, 7H), 7.05-7.10 (m, 1H), 4.97 (s, 1H), 4.61-4.71 (m, 1H), 3.91 (s, 3H), 2.54-2.64 (m, 1H), 2.30-2.44 (m, 3H), 2.24 (s, 2H), 1.55-1.81 (m, 6H), 1.45-1.53 (m, 1H), 1.28-1.36 (m, 1H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  14.05 min.; MS:  $\text{MH}^+$  556.

Example 562: *Cis* N1-[4-(4-amino-1-{4-[(dimethylamino)methyl]-4-

hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(*trans*)-2-phenyl-1-cyclopropanecarboxamide acetate

- To a solution of *cis* N1-[4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-(*trans*)-2-phenylcyclopropane-1-carboxamide (0.190 g, 0.000302 mol) in 2-propanol (10 mL) a 2 M solution of dimethylamine in methanol (0.91 mL) was added and the resulting mixture was heated at 65° C in a pressure tube for 18 hours. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *Cis* N1-[4-(4-amino-1-[4-(dimethylamino)methyl]-4-hydroxycyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(*trans*)-2-phenyl-1-cyclopropanecarboxamide acetate as a white solid (0.109 g, 0.000177 mol):
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.64 (s, 1H), 8.23 (d, 1H), 8.22-8.24 (m, 1H), 7.17-7.33 (m, 7H), 4.56-4.68 (m, 1H), 3.91 (s, 3H), 2.54-2.64 (m, 1H), 2.30-2.44 (m, 3H), 2.28 (s, 6H), 2.24 (s, 2H), 1.91 (s, 3H), 1.63-1.78 (m, 4H), 1.44-1.58 (m, 3H), 1.28-1.36 (m, 1H); RP-HPLC (Delta Pak C18, 5µm, 300Å, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.54 min.; MS: MH<sup>+</sup> 556.

- Example 563: *Trans* N2-(4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(2*R*)tetrahydro-1*H*-2-pyrrolicarboxamide acetate

- A solution of *trans* 3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00046 mol) in *N,N*-dimethylformamide (10 mL) was reacted with 1-hydroxy-7-azabenzotriazole (0.068 g, 0.00050 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.132 g, 0.00069 mol), D-Boc-proline (0.108 g, 0.00050 mol) and *N,N*-diisopropylethylamine (0.184 g, 0.00142 mol) at ambient temperature for 24 hours. The solvent was removed *in vacuo* and the residue was

partitioned between dichloromethane (10 mL) and a 5% aqueous citric acid solution (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (15 mL) and dried over magnesium sulfate.

- 5 The solvent was removed *in vacuo* and the residue was stirred in 20% trifluoroacetic acid in dichloromethane for 6 hours at ambient temperature. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 Å, 25 cm; 5% isocratic for five minutes, then 5%-40% acetonitrile - 0.1M ammonium acetate over 20 min, 21 mL/min). The acetonitrile was removed *in*  
10 *vacuo* and the aqueous mixture was lyophilized to give *trans* N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-(2*R*)tetrahydro-1*H*-2-pyrrolicarboxamide acetate (0.096 g, 0.00016 mol) as a white solid.

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 10.33 (s, 1H), 8.45 (d, 1H), 8.22 (s, 1H), 7.25 (s,  
15 1H), 7.21 (d, 1H), 4.58-4.69 (m, 1H), 3.93 (s, 3H), 3.77 (dd, 1H), 2.96-3.04 (m, 1H), 2.74-2.84 (m, 1H), 2.47-2.58 (m, 5H), 2.23-2.45 (m, 5H), 2.14 (s, 3H), 1.91 (s, 3H), 1.88-2.11 (m, 7H), 1.78-1.88 (m, 1H), 1.60-1.69 (m, 2H), 1.39-1.54 (m, 2H); RP-HPLC (Delta Pak C18, 5µm, 300Å, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 8.47 min.; MS: MH<sup>+</sup> 534.

20

Example 564: 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate

- A. 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate

25

A solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.00 g, 0.019 mol) in *N,N*-dimethylformamide (50 mL) was reacted with 60% sodium hydride in oil (0.92 g, 0.023 mol) at ambient temperature. The mixture was stirred for 15 minutes, and 4-nitropyridine-*N*-oxide (5.37 g, 0.038 mol) was added. The mixture was heated at 100° C. for 18 hours. The precipitate which formed was filtered,  
30 washing with *N,N*-dimethylformamide and ethyl acetate to give 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate (3.79 g, 0.011 mol) as a tan solid:

$^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.38 (s, 1H), 8.34 (d, 2H), 8.24 (d, 2H); RP-HPLC (Delta Pak C18, 5 $\mu\text{m}$ , 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min)  $R_t$  7.36 min.; MS:  $\text{MH}^+$  355.

5            B.    4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate

A suspension of 4-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate (0.140 g, 0.00040 mol) in dimethoxyethane (7 mL) and water (15 mL) was reacted with 4-phenoxyphenylboronic acid (0.093 g, 0.00043 mol), sodium carbonate (0.105 g, 0.00099 mol) and tetrakis(triphenylphosphine) palladium (0) (0.046 g, 0.00004 mol) at 80° C for 18 hours. The solid was filtered to give 4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.138 g, 0.00035 mol) as a brown solid. A portion (0.040 g, 0.00010 mol) was purified by preparative RP-HPLC (Rainin C18, 8 $\mu\text{m}$ , 300 A, 25 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the product 4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate as a white solid (0.013 g, 0.00003 mol).  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.44 (s, 1H), 8.34-8.41 (m, 4H), 7.77 (d, 2H), 7.45 (t, 2H), 7.13-7.24 (m, 5H);  
20            RP-HPLC (Delta Pak C18, 5 $\mu\text{m}$ , 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  14.66 min.; MS:  $\text{MH}^+$  397.

25    Example 565: 3-(4-phenoxyphenyl)-1-(4-pyridyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.100 g, 0.00025 mol) and 10% palladium on carbon (0.016 g, 0.00002 mol) in acetic acid (3 mL) was reacted with sodium hypophosphite monohydrate (0.033 g, 0.00038 mol) at 60° C. After 2 hours, an additional 10% palladium on carbon (0.016 g, 0.00002 mol) was added. The mixture was stirred 18 hours after which time additional 10% palladium on carbon (0.016 g,

0.00002 mol) and sodium hypophosphite monohydrate (0.033 g, 0.00038 mol) was added. The mixture was stirred for an additional 24 hours. The mixture was filtered through Celite ® 521, washing with acetic acid. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 Å, 25 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 ml/min). The acetonitrile was removed in *vacuo* and the aqueous mixture was lyophilized to give 3-(4-phenoxyphenyl)-1-(4-pyridyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.020 g, 0.00005 mol) as a white solid:  
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 8.71 (d, 2H), 8.46 (s, 1H), 8.39 (dd, 2H), 7.78 (d, 2H), 7.46 (t, 2H), 7.13-7.25 (m, 5H); RP-HPLC (Delta Pak C18, 5µm, 300Å, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 20 min, 1 mL/min) R<sub>t</sub> 17.31 min.; MS: MH<sup>+</sup> 381.

Example 566: *N*2-{4-[4-amino-1-(4-pyridyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-2-indolecarboxamide

A. *N*2-{4-[4-amino-1-(4-pyridyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-2-indolecarboxamide

A suspension of 4-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate (0.500 g, 0.0014 mol) in dimethoxyethane (15 mL) and water (30 mL) was reacted with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1H-2-indolecarboxamide (0.631 g, 0.00155 mol), sodium carbonate (0.374 g, 0.0035 mol) and tetrakis(triphenylphosphine) palladium (0) (0.163 g, 0.00014 mol) at 80° C for 18 hours. The solid was filtered and washed with water. The solid was slurried in ethyl acetate for 18 hours and filtered, washing with ethyl acetate. The solid was dried *in vacuo* to give crude 4-[4-amino-3-(3-methoxy-4-[(1-methyl-1H-2-indolyl)-carbonyl]aminophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.523 g, 0.0010 mol) as a brown solid:

RP-HPLC (Delta Pak C18, 5µm, 300Å, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 10 min, 1 mL/min) R<sub>t</sub> 10.92 min.;

MS: MH<sup>+</sup> 507.

B. *N*2-{4-[4-amino-1-(4-pyridyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-

methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

- A suspension of 4-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)carbonyl]amino) phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.200 g, 0.00039 mol) and 10% palladium on carbon (0.042 g, 0.00004 mol) in acetic acid (3 mL) was reacted with sodium hypophosphite monohydrate (0.063 g, 0.00059 mol) at 60° C for 2 hours. Additional 10% palladium on carbon (0.042 g, 0.00004 mol) and sodium hypophosphite (0.045 g, 0.00042 mol) was added and the mixture was stirred for 24 hours. The solvent was removed *in vacuo* and the residue was slurried in methanol for 4 hours. The mixture was filtered through Celite ® 521, washing with methanol. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 Å, 25 cm; 50% isocratic for five minutes, then 50%-100% acetonitrile - 0.1M ammonium acetate over 25 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *N*2-[4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.020 g, 0.00004 mol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.48 (s, 1H) 8.72 (d, 2H), 8.47 (s, 1H), 8.42 (d, 2H), 8.20 (d, 1H), 7.72 (d, 1H), 7.60 (d, 1H), 7.48 (s, 1H), 7.42 (d, 1H), 7.36 (s, 1H) 7.34 (t, 1H), 7.16 (t, 1H), 4.05 (s, 3H), 3.99 (s, 1H); RP-HPLC (Delta Pak C18, 5µm, 300Å, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 19.50 min.; MS: MH<sup>+</sup> 491.

Examples 567: 1-(6-amino-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine; and

- Example 568: 3-(4-phenoxyphenyl)-1-(2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

- A solution of 3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00079 mol) in *N*-methyl pyrrolidinone (10 mL) was reacted with 60% sodium hydride in oil (0.032 g, 0.00079 mol). After gas evolution ceased, the mixture was stirred at ambient temperature for 30 minutes, and 5-bromo-2-nitropyridine (0.161 g, 0.00079 mol) was added and heated at 40° C for 18 hours. Additional 60% sodium hydride in oil (0.032 g, 0.00079 mol) was added and the mixture was stirred an additional 2 hours. The solvent was removed *in vacuo* and the

residue was partitioned between dichloromethane (15 mL) and water (25 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organics were washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica using heptane/ethyl acetate (1:2) as an eluent to give two products. The less polar compound, 1-(6-nitro-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was suspended in absolute ethanol (10 mL) and *N,N*-dimethylformamide (5 mL) and 10% palladium on carbon (0.007 g) was added. The mixture was stirred under a balloon atmosphere of hydrogen for 18 hours. The mixture was filtered through pad of Celite ® 521, washing with absolute ethanol. The solvent was removed *in vacuo* to give 1-(6-amino-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.007 g, 0.00002 mol) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 8.53 (d, 1H) 8.31 (s, 1H), 7.97 (dd, 1H), 7.73 (d, 2H), 7.44 (t, 2H), 7.12-23 (m, 5H), 6.60 (d, 1H), 6.20 (s, 2H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 15.38 min.; MS: MH<sup>+</sup> 396.

The more polar compound, 3-(4-phenoxyphenyl)-1-(5-bromo-2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was suspended in absolute ethanol (10 mL) and *N,N*-dimethylformamide (5 mL) and 10% palladium on carbon (0.007 g) was added. The mixture was stirred under a balloon atmosphere of hydrogen for 18 hours. The mixture was filtered through pad of Celite ® 521, washing with absolute ethanol. The solvent was removed *in vacuo* to give 3-(4-phenoxyphenyl)-1-(2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.030 g, 0.00007 mol) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 8.60-8.64 (m, 1H) 8.37 (s, 1H), 8.20 (d, 1H), 8.03-8.08 (m, 1H), 7.76 (d, 2H), 7.41-7.49 (m, 3H), 7.12-7.23 (m, 5H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 16.32 min.; MS: MH<sup>+</sup> 381.

30

A general procedure for reductive amination using *trans*-3-(4-amino-phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as



starting material and an aldehyde is described in Example 569. Various other aldehydes can be substituted for 2-methoxy-3-formyl-pyridine of Example 569 to attach other Z<sup>100</sup> groups.

- 5    Examples 569:    *trans*-3-[4-[(2-methoxy-3-pyridyl)methyl]aminophenyl]-1-[4-(4-methyl-piperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate; and

A mixture of *trans*-3-(4-amino-phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1 eq.), 2-methoxy-3-formyl-pyridine (1.05 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, quenched with saturated solution of sodium bicarbonate in water and concentrated again. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired products. The following two compounds were prepared according to the procedure above:

*trans*-3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 8.18 (s, 1H), 8.06 (dd, 1H), 7.61 (d, 1H), 7.35 (d, 2H), 6.95 (dd, 1H), 6.69 (d, 2H), 6.51 (t, 1H), 4.60 (m, 1H), 4.26 (d, 2H), 3.94 (s, 3H), 2.64 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.07 min.

MS: MH<sup>+</sup> 528.

- Example 570: *trans*-3-{4-[(1*H*-2-indolylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
- Trans*-3-{4-[(1*H*-2-indolylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate was prepared as in the method of Example 569 except that 2-formyl-indole was used instead of 2-methoxy-3-formyl-pyridine.

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  11.08 (s, 1H), 8.19 (s, 1H), 7.44 (d, 1H), 7.36 (d, 2H), 7.32 (d, 1H), 7.01 (t, 1H), 6.95 (t, 1H), 6.81 (d, 2H), 6.47 (t, 1H), 6.35 (s, 1H), 4.60 (m, 1H), 4.45 (d, 2H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.74 min.
- MS: MH<sup>+</sup> 536.

- Example 571: *Trans*-3-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)methyl]-1,2-dihydro-2-pyridinone diacetate
- Trans*-3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.105 g, 0.000199mol) was dissolved in 30% hydrogen bromide in acetic acid (4 mL) and the mixture was refluxed for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)methyl]-1,2-dihydro-2-pyridinone diacetate (0.0204 g, 0.0000324 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.18 (s, 1H), 7.29 (m, 4H), 6.68 (d, 2H), 6.40 (t, 1H), 6.15 (m, 1H), 4.60 (m, 1H), 4.09 (d, 2H), 2.64 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 9.40 min. MS: MH<sup>+</sup> 514.

- A general procedure for reductive amination with *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine and an aldehyde as starting material is described in Example 572:

Example 572: *Trans*-5-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyanilino)methyl]-4-chloro-1,3-thiazol-2-amine diacetate

5           A mixture of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1 eq.), 2-amino-4-chloro-5-formyl-1,3-thiazole (1.05 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, quenched  
10       with saturated solution of sodium bicarbonate in water and concentrated again. The residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired product.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.19 (s, 2H), 7.06 (m, 3H), 6.68 (d, 1H),  
15       5.76 (t, 1H), 4.60 (m, 1H), 4.30 (d, 2H), 3.85 (s, 3H), 2.6-2.2 (br, 9H), 2.17 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.59 min.

MS: MH<sup>+</sup> 583.

20

Examples 573 and 574 were prepared according to the method of Example 572:

Example 573: *Trans*-3-(3-methoxy-4-[(5-methyl-3-isoxazolyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate  
25           amine acetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.04 (m, 2H), 6.68 (d, 1H), 6.16 (s, 1H),  
5.86 (t, 1H), 4.60 (m, 1H), 4.37 (d, 2H), 3.86 (s, 3H), 2.6-2.2 (br, 9H), 2.40 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.53 min.  
30

MS: MH<sup>+</sup> 532.

Example 574: *Trans*-3-{3-methoxy-4-[(1,3-thiazol-4-ylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.08 (s, 1H), 8.19 (s, 1H), 7.47 (s, 1H), 7.06 (s, 1H), 7.03 (d, 1H), 6.68 (d, 1H), 5.76 (t, 1H), 4.60 (m, 1H), 4.52 (d, 2H), 3.88 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.17 min.

MS: MH<sup>+</sup> 534.

A general procedure for the synthesis of benzotetrahydrofuran-derivatives with *trans*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and a 2-hydroxybenzaldehyde as starting materials is given in Example 575.

Example 575: *Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

*Trans*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1 equiv., 0.0001–0.0002 mol scale) and 2-hydroxy-4,6-dichlorobenzaldehyde (1 equiv.) were combined in absolute ethanol (5 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was concentrated under reduced pressure and the residue dried overnight to yield the corresponding imine, which was used without further purification.

Trimethylsulfoxonium iodide (2.5 equiv.) was dissolved in anhydrous dimethylsulfoxide (2 mL) and a 60% dispersion of sodium hydride in paraffin (2.5 equiv.) was added at once. After 10 min., the solution of the imine in anhydrous dimethylsulfoxide (2 mL) was added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 2.5 hours. The solution was poured into ice-cold water (50 mL) and extracted with dichloromethane (2x40 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25

min, 21mL/min) to yield the final compound.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.39 (d, 2H), 7.14 (s, 1H), 7.07 (s, 1H), 6.80 (d, 2H), 6.56 (d, 1H), 5.34 (m, 1H), 4.80 (dd, 1H), 4.60 (m, 1H), 4.42 (dd, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

- 5 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 16.03 min.  
MS: MH<sup>+</sup> 593.

- Example 576: *Trans*-3-{4-[(4-chloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
- 10

- Trans*-3-{4-[(4-chloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate was prepared using the method of Example 575 except 2-hydroxy-4,6-dichlorobenzaldehyde was replaced with 2-hydroxy-4-chlorobenzaldehyde.
- 15

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.39 (d, 2H), 7.28 (t, 1H), 6.99 (d, 1H), 6.89 (d, 1H), 6.81 (d, 2H), 6.53 (d, 1H), 5.34 (m, 1H), 4.74 (dd, 1H), 4.60 (m, 1H), 4.38 (dd, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
- 20 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.42 min.  
MS: MH<sup>+</sup> 559.

- Example 577: *Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]-3-methoxyphenyl-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
- 25

- Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]-3-methoxyphenyl-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate was prepared using the method of Example 575 except
- 30 *trans*- 3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine was used instead of *trans*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.11 (m, 4H), 6.80 (d, 1H), 5.45(m, 2H), 4.84 (dd, 1H), 4.60 (m, 1H), 4.42 (dd, 1H), 3.82 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

5 ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 16.85 min.

MS: MH<sup>+</sup> 623.

Intermediate 5: *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

10

A. *Tert*-butyl 4-[4-amino-3-(4-[(benzyloxy)carbonyl]aminophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

A mixture of benzyl *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-phenyl)]carbamate (9.54 g, 0.027 mol), *tert*-butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (10.0 g, 0.0225 mol),  
15 tetrakis-(triphenylphosphine)palladium (1.56 g, 0.00135 mol) and sodium carbonate (5.97 g, 0.0563 mol) was heated in a mixture of ethylene glycol dimethyl ether (120 mL) and water (60 mL) at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed  
20 under the reduced pressure. The residue was partitioned between water (150 mL) and dichloromethane (150 mL); the organic phase was washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was triturated in diethyl ether and the precipitate was collected by filtration and dried to yield *tert*-butyl 4-[4-amino-3-(4-[(benzyloxy)carbonyl]aminophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (10.1 g, 0.0186 mol) as a  
25 white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.00 (s, 1H), 8.23 (s, 1H), 7.64 (d, 2H), 7.43 (d, 2H), 7.36 (m, 5H), 5.18 (s, 2H), 4.90 (m, 1H), 4.08 (br, 2H), 3.00 (br, 2H), 2.02 (m, 4H), 1.42 (s, 9H);

30 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 18.58 min.

B. *Tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

- To a solution of *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (5.0 g, 0.0092 mol) in tetrahydrofuran (150 mL) 10% palladium on carbon (1.0 g) was added and the reaction mixture was hydrogenated on a Parr shaker over 96 hours. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was triturated in *n*-heptane and the precipitate was collected by filtration and dried to yield *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (2.51 g, 0.0061 mol) as an off-white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.35 (d, 2H), 6.69 (d, 2H), 5.42 (s, 2H), 4.90 (m, 1H), 4.08 (br, 2H), 3.00 (br, 2H), 2.02 (m, 4H), 1.42 (s, 9H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.18 min.

Example 578-590:

A general procedure for reductive amination followed by BOC deprotection that was used to prepare Examples 578-590 is given below:

20

Protocol:

- A mixture of *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (Intermediate 5) (1 eq.), an aldehyde (1.2 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, triturated in ethyl acetate and treated with a 4N aqueous solution of hydrochloric acid. The resulting mixture was stirred for 1 hour; aqueous phase was neutralized with saturated solution of sodium bicarbonate in water and the layers separated. Organic phase was concentrated under reduced pressure and the residue was purified by preparative HPLC ( Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired products.

30

The following compounds were made using the above procedure:

Example 578: 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

- 5 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.57 (d, 1H), 7.53 (d, 1H), 7.39 (d, 2H), 7.23 (m, 2H), 6.85 (d, 2H), 6.80 (s, 1H), 6.66 (t, 1H), 4.70 (m, 1H), 4.51 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.37 min.

- 10 MS: MH<sup>+</sup> 440.

Example 579: 3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 8.06 (d, 1H), 7.61 (d, 1H), 7.36 (d, 15 2H), 6.96 (dd, 1H), 6.69 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.27 (d, 2H), 3.94 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.06 min.

MS: MH<sup>+</sup> 431.

20

Example 580: 3-(4-[(5-methyl-2-thienyl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.36 (d, 2H), 6.85 (d, 1H), 6.77 (d, 2H), 6.64 (d, 1H), 6.54 (t, 1H), 4.70 (m, 1H), 4.41 (d, 2H), 3.07 (m, 2H), 2.65 (m, 25 2H), 2.38 (s, 3H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.85 min.

MS: MH<sup>+</sup> 420.

- 30 Example 581: 3-{4-[(2-furylmethyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.59 (s, 1H), 7.36 (d, 2H), 6.77 (d,



2H), 6.46 (t, 1H), 6.39 (d, 1H), 6.34 (d, 1H), 4.70 (m, 1H), 4.31 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 10.96 min.

5 MS: MH<sup>+</sup> 390.

Example 582: 3-[4-(benzylamino)phenyl]-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.34 (m, 6H), 7.24 (t, 1H), 6.73 (d, 2H), 6.60 (t, 1H), 4.70 (m, 1H), 4.33 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.32 min.

MS: MH<sup>+</sup> 400.

15

Example 583: 3-{4-[(2-methoxybenzyl)amino]phenyl}-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.35 (d, 2H), 7.24 (m, 2H), 7.01 (d, 1H), 6.90 (t, 1H), 6.70 (d, 2H), 6.41 (t, 1H), 4.70 (m, 1H), 4.28 (d, 2H), 3.85 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.73 min.

MS: MH<sup>+</sup> 430.

25 Example 584: 3-{4-[(3-methoxybenzyl)amino]phenyl}-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 6.96 (m, 2H), 6.81 (d, 1H), 6.72 (d, 2H), 6.59 (t, 1H), 4.70 (m, 1H), 4.30 (d, 2H), 3.74 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

30 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.38 min.

MS: MH<sup>+</sup> 430.

Example 585: 3-[4-[(4-methoxybenzyl)amino]phenyl]-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.35 (m, 4H), 6.90 (d, 2H), 6.72 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.25 (d, 2H), 3.73 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.37 min.

MS: MH<sup>+</sup> 430.

10

Example 586: 1-(4-piperidyl)-3-(4-[3-(trifluoromethyl)benzyl]aminophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.71 (m, 2H), 7.58 (m, 2H), 7.36 (d, 2H), 6.72 (m, 3H), 4.70 (m, 1H), 4.44 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.08 min.

MS: MH<sup>+</sup> 468.

20 Example 587: 1-(4-piperidyl)-3-(4-[4-(trifluoromethyl)benzyl]aminophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.70 (d, 2H), 7.60 (d, 2H), 7.36 (d, 2H), 6.72 (m, 3H), 4.70 (m, 1H), 4.44 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

25 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.23 min.

MS: MH<sup>+</sup> 468.

Example 588: 3-(4-[(2-methyl-1,3-thiazol-4-yl)methyl]aminophenyl)-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

30

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.41 (d, 2H), 7.26 (s, 1H), 6.73 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.36 (d, 2H), 3.07 (m, 2H), 2.70 (s, 3H), 2.65 (m,

2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 10.13 min.

MS: MH<sup>+</sup> 421.

5

Example 589: 3-{4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.42 (m, 4H), 7.26 (t, 1H), 6.83 (d, 2H), 6.27 (t, 1H), 4.72 (m, 1H), 4.37 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

10

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.32 min.

MS: MH<sup>+</sup> 452.

15

Example 590: 3-(4-[2-fluoro-4-(trifluoromethyl)benzyl]aminophenyl)-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.61 (m, 3H), 7.38 (d, 2H), 6.73 (d, 2H), 6.68 (t, 1H), 4.70 (m, 1H), 4.47 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

20

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.83 min.

MS: MH<sup>+</sup> 486.

Example 591: 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]-3-methoxyphenyl}-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine diacetate

25

A mixture of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinecarboxylate (g, mol), benzofuran-2-carbaldehyde (0.046 g, 0.000315 mol), sodium triacetoxyborohydride (0.089 g, 0.00042 mol.) and acetic acid (0.024 mL, 0.00042 mol) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, triturated in ethyl acetate (4mL) and treated with a 4N aqueous solution of hydrochloric acid (1 mL). The resulting mixture was stirred for 1 hour; aqueous

30

phase was neutralized with saturated solution of sodium bicarbonate in water and the layers separated. The organic phase was concentrated under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60%

- 5 [(benzo[*b*]furan-2-ylmethyl)amino]-3-methoxyphenyl]-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.027 g, 0.0000457 mol).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.55 (m, 2H), 7.22 (m, 2H), 7.06 (m, 2H), 6.80 (d, 1H), 6.75 (s, 1H), 5.80 (t, 1H), 4.70 (m, 1H), 4.57 (d, 2H), 3.89 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

- 10 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.83 min.

MS: MH<sup>+</sup> 470.

Example 592: 3-[4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)phenyl]-1-(4-piperidyl)-

- 15 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

Salicylaldehyde (0.063 g, 0.000513 mol) and *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.200 g, 0.000489 mol) were combined in absolute ethanol (5 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was concentrated under reduced

20 pressure and the residue dried overnight to yield *tert*-butyl 4-[4-amino-3-(4-[[1-(2-hydroxyphenyl)methylidene]amino}phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate which was used without further purification.

Trimethylsulfoxonium iodide (0.269 g, 0.00122 mol) was dissolved in anhydrous dimethylsulfoxide (2 mL) and a 60% dispersion of sodium hydride in paraffine

- 25 (0.049 g, 0.00122 mol) was added at once. After 10 min., the solution of *tert*-butyl 4-[4-amino-3-(4-[[1-(2-hydroxyphenyl)methylidene]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate in anhydrous dimethylsulfoxide (2 mL) was added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 2.5 hours. The solution was poured into ice-cold water
- 30 (70 mL) and extracted with dichloromethane (2x50 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure to yield crude *tert*-butyl 4-[4-amino-3-[4-(2,3-dihydrobenzo[*b*]furan-3-

- ylamino)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinecarboxylate which was used without further purification. The crude compound was dissolved in ethyl acetate (5 mL) and treated with a 4N aqueous solution of hydrochloric acid (1.5 mL). The resulting emulsion was vigorously stirred for 1 hour; the water layer was
- 5 neutralized with saturated solution of sodium bicarbonate in water and the layers were separated. The organic phase was concentrated under reduced pressure and residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield 3-[4-(2,3-dihydrobenzo[b]furan-3-ylamino)phenyl]-1-(4-piperidyl)-1H-pyrazolo[3,4-
- 10 d]pyrimidin-4-amine acetate (0.038g, 0.000078 mol) as a white solid
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.41 (m, 3H), 7.25 (t, 1H), 6.89 (m, 4H), 6.51 (t, 1H), 5.35 (m, 1H), 4.79 (m, 2H), 4.27 (m, 1H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 3H), 1.79 (m, 2H);
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M
- 15 ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.38 min.
- MS: MH<sup>+</sup> 428.

- Example 593: *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}anilino)-1H-1 $\lambda$ <sup>6</sup>-benzo[d]isothiazole-
- 20 1,1-dione acetate

A. 3-chloro-1H-1 $\lambda$ <sup>6</sup>-benzo[d]isothiazole-1,1-dione

- Saccharin (10.0 g, 0.0546 mol) and phosphorus pentachloride (12.6 g, 0.060mol) were heated at 170°C for 1.5 hours. The reaction mixture was cooled to
- 25 ambient temperature and suspended in diethyl ether (200 mL). The precipitate was collected by filtration, thoroughly washed with diethyl ether and dried to yield 3-chloro-1H-1 $\lambda$ <sup>6</sup>-benzo[d]isothiazole-1,1-dione (3.7 g, 0.0184 mol) as a white solid which was used without further purification.
- MS: MH<sup>+</sup> 202.

30

B. 3-(4-bromoanilino)-1H-1 $\lambda$ <sup>6</sup>-benzo[d]isothiazole-1,1-dione

To a solution of 3-chloro-1H-1 $\lambda$ <sup>6</sup>-benzo[d]isothiazole-1,1-dione (1.0 g, 0.00496

mol) in acetone (20 mL), 4-bromoaniline (1.71 g, 0.00992 mol) was added at once and the mixture was stirred for 15 min. The mixture was concentrated under reduced pressure and the residue was suspended in water (100 mL). The precipitate was collected by filtration, thoroughly washed with water and dried to yield 3-(4-bromoanilino)-1*H*-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione (1.57 g, 0.00467 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 10.93 (s, 1H), 8.47 (d, 1H), 8.09 (d, 1H), 7.93 (m, 4H), 7.69 (d, 2H);

10 C. 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ<sup>6</sup>-benzo[*d*] isothiazole-1,1-dione

A mixture of 3-(4-bromoanilino)-1*H*-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione (1.57 g, 0.00467 mol), diboron pinacol ester (1.43 g, 0.00561 mol), [1,1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with 15 dichloromethane (1:1) (0.114 g, 0.00014 mol) and potassium acetate (1.37 g, 0.014 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. 20 The filtrate was concentrated to leave a yellow oil that was triturated in diethyl ether to yield 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ<sup>6</sup>-benzo[*d*] isothiazole-1,1-dione (1.14 g, 0.00297 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 10.92 (br, 1H), 8.51 (d, 1H), 8.08 (d, 1H), 7.91 (m, 4H), 7.68 (d, 2H), 1.29 (s, 12H).

25

D. *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione acetate

A mixture of 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ<sup>6</sup>-benzo[*d*] isothiazole-1,1-dione (0.09 g, 0.000234 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.08 g, 0.00018 mol), tetrakis-(triphenylphosphine)palladium (0.013 g, 0.000011 mol) and sodium

30

carbonate (0.048 g, 0.00045 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1H-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione acetate (0.075 g, 0.000119 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 8.29 (d, 1H), 8.23 (s, 1H), 7.91 (m, 3H), 7.79 (m, 2H), 7.66 (d, 2H), 4.65 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.27 min.

MS: MH<sup>+</sup> 572.

15

Example 594: *Cis*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1H-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione diacetate

*Cis*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1H-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione diacetate was prepared from 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1H-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione (0.09 g, 0.000234 mol) and *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine by a similar protocol as described above.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 8.42 (d, 1H), 8.23 (s, 1H), 7.91 (m, 3H), 7.84 (m, 2H), 7.62 (d, 2H), 4.80 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.07 (m, 4H), 1.91 (s, 6H), 1.65(m, 2H), 1.58 (m, 2H);

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.59 min.

30 MS: MH<sup>+</sup> 572.

Example 595: *Trans*-N3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-

pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine  
acetate

A. *N*1-(4-bromophenyl)-2-fluorobenzamide

5 A solution of 2-fluorobenzoyl chloride (5.82 g, 0.0367 mol) and 4-bromoaniline (6.31 g, 0.0367 mol) in anhydrous dichloromethane (150 mL) was cooled to 0°C and *N,N*-diisopropylethylamine (5.21 g, 0.0407 mol) was added under nitrogen atmosphere dropwise. The resulting mixture was stirred at ambient temperature for 24 hours, concentrated and the residue partitioned between ethyl acetate (120 mL) and water (100  
10 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold diethyl ether (50 mL) and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluorobenzamide (9.6 g, 0.0326 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.54 (s, 1H), 7.66 (m, 3H), 7.56 (m, 3H), 7.34 (m,  
15 2H). TLC (ethyl acetate / heptane 1:2) R<sub>f</sub> 0.37

B. *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide

A mixture of *N*1-(4-bromophenyl)-2-fluorobenzamide (3.3 g, 0.0112 mol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (2.27 g,  
20 0.00561 mol) was heated in toluene at reflux under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica using ethyl acetate/*n*-heptane (1:6) as mobile phase to yield *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (3.1 g, 0.010 mol) as a  
25 yellow solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  12.13 (s, 1H), 7.93 (d, 2H), 7.62 (m, 3H), 7.51 (m, 1H), 7.31 (m, 2H). TLC (ethyl acetate / heptane 1:4) R<sub>f</sub> 0.27

C. *N*1-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime

30 A mixture of *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (1.56 g, 0.00505 mol), hydroxylamine hydrochloride (0.44 g, 0.00631 mol) and sodium bicarbonate (0.53 g, 0.00631 mol) was heated in absolute ethanol (25 mL) at reflux



under nitrogen atmosphere for 14 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold diethyl ether and the precipitate was collected by filtration and dried to yield *N*-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime (1.21 g, 0.00392 mol) as an off-white solid.

TLC (ethyl acetate / heptane 1:4)  $R_f$  0.12

D. *N*-benzo[*d*]isoxazol-3-yl-*N*-(4-bromophenyl)amine

To a solution of *N*-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime (1.51 g, 0.00489 mol) in *N*-methylpyrrolidinone (25 mL), potassium *tert*-butoxide (0.54 g, 0.00513 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate/ *n*-heptane (1:5) as mobile phase to yield *N*-benzo[*d*]isoxazol-3-yl-*N*-(4-bromophenyl)amine (0.95 g, 0.00329 mol) as a white solid.

$^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  9.72 (s, 1H), 8.13 (d, 1H), 7.68 (d, 2H), 7.61 (m, 2H), 7.54 (d, 2H), 7.37 (dd, 1H).

TLC (ethyl acetate / heptane 1:4)  $R_f$  0.26

E. *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine

A mixture of *N*-benzo[*d*]isoxazol-3-yl-*N*-(4-bromophenyl)amine (1.30 g, 0.0045 mol), diboron pinacol ester (1.37 g, 0.0054 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.110 g, 0.000135 mol) and potassium acetate (1.32 g, 0.0135 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80°C under an

- atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was
- 5 purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield *N*-benzo[d]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.40 g, 0.00119 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.74 (s, 1H), 8.16 (d, 1H), 7.70 (m, 4H), 7.61 (d, 2H), 7.37 (dd, 1H), 1.29 (s, 12H).
- 10 TLC (ethyl acetate / heptane 1:4) R<sub>f</sub> 0.21

F. *Trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[d]isoxazol-3-amine acetate

- A mixture of *N*-benzo[d]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.10 g, 0.000298 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.101 g, 0.000229 mol), tetrakis-(triphenylphosphine)palladium (0.016 g, 0.0000137 mol) and sodium carbonate (0.061 g, 0.000573 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80°C for 16 hours under an
- 20 atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-
- 25 yl}phenyl)benzo[d]isoxazol-3-amine acetate (0.102 g, 0.000175 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.81 (s, 1H), 8.23 (s, 1H), 8.19 (d, 1H), 7.88 (d, 2H), 7.65 (m, 4H), 7.40 (m, 1H), 4.65 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
- 30 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.66 min.
- MS: MH<sup>+</sup> 524.

Example 596: *Cis-N3*-[4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine diacetate

- 5        *Cis-N3*-[4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine diacetate was prepared from *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine and *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine by a similar protocol as described above.
- 10        <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.86 (s, 1H), 8.26 (s, 1H), 8.24 (d, 1H), 7.93 (d, 2H), 7.67 (m, 4H), 7.43 (m, 1H), 4.83 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.08 (m, 4H), 1.91 (s, 6H), 1.74 (m, 2H), 1.62 (m, 2H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.77 min.
- 15        MS: MH<sup>+</sup> 524.

Example 597: *N3*-[4-{4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl]benzo[*d*]isoxazol-3-amine acetate

- 20        A mixture of *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.087 g, 0.000258 mol), *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (0.088 g, 0.000198 mol), tetrakis-(triphenylphosphine)palladium (0.014 g, 0.000012 mol) and sodium carbonate (0.053 g, 0.000495 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere
- 25        of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure and the residue partitioned between water and dichloromethane. The organic phase was dried with magnesium sulfate and concentrated under reduced pressure to yield crude *tert*-butyl 4-{4-amino-3-[4-(benzo[*d*]isoxazol-3-ylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}-1-
- 30        piperidinecarboxylate which was used without further purification. It was dissolved in ethyl acetate (5 mL) and treated with a 4*N* aqueous solution of hydrochloric acid (1 mL). The resulting emulsion was vigorously stirred for 1 hour; the water layer

was neutralized with saturated solution of sodium bicarbonate in water and the layers were separated. The organic phase was concentrated under reduced pressure and residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield N3-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}benzo[d]isoxazol-3-amine acetate (0.009g, 0.0000185 mol) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.82 (s, 1H), 8.20 (m, 2H), 7.89 (d, 2H), 7.65 (m, 4H), 7.41 (t, 1H), 4.74 (m, 1H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 3H), 1.79 (m, 2H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.20 min. MS: MH<sup>+</sup> 427.

Example 598: *Trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A. N1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide  
N1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (1.50 g, 0.00485 mol) and a 1M solution of hydrazine in tetrahydrofuran (6.3 mL, 0.0063 mol) were heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. Additional 3 mL of a 1M solution of hydrazine in tetrahydrofuran was added and the stirring at reflux was continued for another 6 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated to yield N1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide (1.54 g, 0.0050 mol) as a tan solid.. TLC (ethyl acetate / heptane 1:3) R<sub>f</sub> 0.10

B. N-(4-bromophenyl)-N-(1*H*-3-indazolyl)amine

To a solution of N1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide (1.2 g, 0.00391 mol) in *N*-methyl pyrrolidinone (25 mL), potassium *tert*-butoxide (0.50 g, 0.0041 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under

reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine (0.29 g, 0.0010 mol) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  12.06 (s, 1H), 9.03 (s, 1H), 7.93 (d, 1H), 7.65 (d, 2H), 7.35 (m, 4H), 7.03 (dd, 1H). TLC (ethyl acetate / heptane 1:3) R<sub>f</sub> 0.26

- 10 C. *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine

A mixture of *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine (0.29 g, 0.00101 mol), diboron pinacol ester (0.31 g, 0.00121 mol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.025 g, 0.00003 mol) and potassium acetate (0.294 g, 0.003 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:3) as mobile phase to yield *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.064 g, 0.000191 mol) as an off-white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  12.09 (s, 1H), 9.06 (s, 1H), 7.94 (d, 1H), 7.64 (d, 2H), 7.57 (d, 2H), 7.35 (m, 2H), 7.03 (dd, 1H), 1.28 (s, 12H). TLC (ethyl acetate / heptane 1:3) R<sub>f</sub> 0.21

- D. *Trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A mixture of *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.064 g, 0.000191 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.070 g, 0.000159 mol), tetrakis-(triphenylphosphine)palladium (0.011 g, 0.0000095 mol) and sodium carbonate (0.042

g, 0.000398 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.035 g, 0.000060 mol) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 12.09 (s, 1H), 9.14 (s, 1H), 8.21 (s, 1H), 7.99 (d, 1H), 7.83 (d, 2H), 7.55 (d, 2H), 7.37 (m, 2H), 7.06 (t, 1H), 4.64 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.49 (m, 2H); RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.96 min. MS: MH<sup>+</sup> 523.

- 15 Example 599: *Trans*-N3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate

A. N1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide

- 20 A solution of 2-fluoro-4-(trifluoromethyl)benzoyl chloride (5.05 g, 0.0223 mol) and 4-bromoaniline (3.83 g, 0.0223 mol) in anhydrous dichloromethane (150 mL) was cooled to 0°C and *N,N*-diisopropylethylamine (4.26 mL, 0.0245 mol) was added under nitrogen atmosphere dropwise. The resulting mixture was stirred at ambient temperature for 24 hours, concentrated and the residue was partitioned between ethyl acetate (120 mL) and water (100 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold *n*-heptane (50 mL) and the precipitate was collected by filtration and dried to yield N1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide (7.1 g, 0.0196 mol) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 10.74 (s, 1H), 7.90 (m, 2H), 7.74 (d, 1H), 7.68 (d, 2H), 7.56 (d, 2H).

B. N1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-

## benzenecarbothioamide

- A mixture of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide (7.1 g, 0.0196 mol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphatane-2,4-disulfide (3.97 g, 0.0098 mol) was heated in toluene at reflux under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica using ethyl acetate/n-heptane (1:8) as mobile phase to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide (6.0 g, 0.0159 mol) as a yellow solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  12.33 (s, 1H), 7.94 (d, 2H), 7.81 (m, 2H), 7.65 (m, 3H). TLC (ethyl acetate / heptane 1:4) *R*<sub>f</sub> 0.61

C. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime

- A mixture of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide (2.50 g, 0.00663 mol), hydroxylamine hydrochloride (0.65 g, 0.00928 mol) and sodium bicarbonate (0.78 g, 0.00928 mol) was heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold n-heptane and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime (2.35 g, 0.00625 mol) as an off-white solid.
- TLC (ethyl acetate / heptane 1:4) *R*<sub>f</sub> 0.12

D. *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine

- To a solution of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime (2.25 g, 0.00598 mol) in *N*-methylpyrrolidinone (30 mL), potassium *tert*-butoxide (0.71 g, 0.00628 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction

mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold n-heptane and the precipitate was collected by filtration and dried to yield *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine (1.75 g, 0.0049 mol) as an off-white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.95 (s, 1H), 8.37 (d, 1H), 8.14 (s, 1H), 7.78 (d, 1H), 7.68 (d, 2H), 7.58 (d, 2H). TLC (ethyl acetate / heptane 1:5) R<sub>f</sub> 0.31

E. *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine

A mixture of *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine (1.75 g, 0.0049 mol), diboron pinacol ester (1.49 g, 0.0059 mol), [1,1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.120 g, 0.000147 mol) and potassium acetate (1.44 g, 0.0144 mol) in *N,N*-dimethylformamide (10 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:6) as mobile phase to yield *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine

(0.065 g, 0.000161 mol) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.97 (s, 1H), 8.39 (d, 1H), 8.14 (s, 1H), 7.77 (d, 1H), 7.71 (s, 4H), 1.29 (s, 12H).

F. *Trans*-*N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[d]isoxazol-3-amine acetate

A mixture of *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine (0.062 g, 0.000153 mol), *trans*-3-



- iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.065 g, 0.000146 mol), tetrakis-(triphenylphosphine)palladium (0.010 g, 0.000087 mol) and sodium carbonate (0.039 g, 0.000365 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80 °C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-70% acetonitrile – 0.1M ammonium acetate over 30 min, 21mL/min) to yield *trans*-*N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate (0.026 g, 0.0000398 mol) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 10.05 (s, 1H), 8.44 (d, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.88 (d, 2H), 7.79 (d, 1H), 7.69 (d, 2H), 4.67 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H); RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 16.18 min. MS: MH<sup>+</sup> 592.

Example 600: *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

20

A. 3-iodo-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

- To a mixture of 3-iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (0.4 g, 0.00096 mol) and potassium carbonate (0.40 g, 0.0029 mol) in *N,N*-dimethylformamide (25 mL) was added 2-bromoethyl methyl ether (0.09 mL, 0.00096 mol) at room temperature. The heterogeneous mixture was stirred at 60 °C under an atmosphere of nitrogen for 7 hours. The reaction mixture was cooled to room temperature, and 2-bromoethyl methyl ether (0.045 mL, 0.00048 mol) was added. The mixture was stirred at 60 °C under an atmosphere of nitrogen for 16 hours. To the mixture to the room temperature, 2-bromoethyl methyl ether (0.019 mL, 0.00019 mol) and potassium iodide (0.008 g, 0.000048 mol) were added in order to complete the reaction. The mixture was stirred at 70 °C under an

30

atmosphere of nitrogen for 7 hours. The solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (4 x 50 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 $\mu$ m, 250 x 21.1 mm; 5% - 50% over 30 min with 0.1 M ammonium acetate, 21mL/min) to yield 3-iodo-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.2 g, 0.0005 mol). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 10 min, 1mL/min) Rt 6.4 min. MS: MH<sup>+</sup> 403

B. *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A mixture of 3-iodo-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.2 g, 0.0005 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.28 g, 0.00078 mol), tetrakis(triphenylphosphine)palladium (0.029 g, 0.000025 mol) and sodium carbonate (0.13 g, 0.00125 mol) in ethylene glycol dimethyl ether (25 mL) and water (5 mL) was heated at 80°C for 5 hours under an atmosphere of nitrogen. Additional *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.14 g, 0.00039 mol.) and tetrakis(triphenylphosphine)-palladium (0.015 g, 0.0000125 mol) were added, and the mixture was stirred at 80 °C for 16 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 5 % - 20 % methanol / dichloromethane as a mobile phase to give *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-

- yl]phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.14 g, 0.00027 mol). <sup>1</sup>H NMR (TFA-*d*, 400 MHz)  $\delta$  8.53 (s, 1H), 7.88 (m, 2H), 7.81 (m, 2H), 7.14 (s, 2H), 5.40 (br, 1H), 4.05 (m, 2H), 3.98 (m, 2H), 3.66 (m, 2H), 3.56 (s, 3H), 3.47 (m, 2H), 2.96 (m, 2H), 2.54 (br, 2H), 2.50 (s, 3H), 2.43 (s, 3H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.6 min. MS: MH<sup>+</sup> 513

Example 601: *N*2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

- 10 A. 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a mixture of 3-iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (0.5 g, 0.0012 mol) and sodium triacetoxyborohydride (0.36 g, 0.00168 mol) in dichloroethane (40 mL) was added formaldehyde solution (37 % in water, 0.037 mL, 0.00132 mol) at room temperature. The mixture was stirred at room temperature under an atmosphere of nitrogen for 4 hours. A 5 N aqueous solution of sodium hydroxide (2 mL) was added to the mixture. The solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave solid. The solid was resubjected to the same reaction and work-up conditions as above to yield 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.3 g, 0.00084 mol). TLC (methanol / dichloromethane = 10 : 20 90) R<sub>f</sub> 0.63 MS: MH<sup>+</sup> 359

B. *N*2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

- 30 A mixture of 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.2 g, 0.00056 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*'-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.2 g, 0.00056 mol), tetrakis(triphenylphosphine)-palladium (0.032 g, 0.000028 mol) and sodium

carbonate (0.15 g, 0.0014 mol) in ethylene glycol dimethyl ether (20 mL) and water (5 mL) was heated at 80°C for 3 hours under an atmosphere of nitrogen. Additional *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.2 g, 0.00056 mol) and tetrakis(triphenylphosphine)palladium (0.032 g, 0.00028 mol) were added, and the mixture was stirred at 80 °C for 16 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 5 % - 25 % methanol / dichloromethane as a mobile phase to give *N*2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine (0.16 g, 0.00034 mol). <sup>1</sup>H NMR (TFA-*d*, 400 MHz)  $\delta$  8.50 (s, 1H), 7.85 (m, 2H), 7.80 (m, 2H), 7.10 (s, 2H), 5.45 (br, 1H), 3.95 (br, 2H), 3.75 (br, 1H), 3.45 (br, 1H), 3.10 (s, 3H), 2.85 (br, 1H), 2.65 (br, 1H), 2.49 (br, 2H), 2.40 (s, 3H), 2.42 (s, 3H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) Rt 10.7 min. MS: MH<sup>+</sup> 469

20

Example 602: *N*2-{4-[4-amino-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

A. 3-Iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine

Diethyl azodicarboxylate (12 mL, 0.08 mol) was added to a stirred suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (10.44 g, 0.04 mol), *tert*-butyl 3-hydroxy-1-piperidinecarboxylate (12.0 g, 0.0596 mol), and triphenylphosphine (20.98 g, 0.08 mol) in tetrahydrofuran (600 mL) at room temperature. After 19 h, additional diethyl azodicarboxylate (12 mL, 0.08 mol) was added and the reaction was continued for a further 2 h. Additional *tert*-butyl 3-hydroxy-1-piperidinecarboxylate (2.0 g) and triphenylphosphine (20.98 g, 0.08 mol) were added and the reaction continued for a further 72 h.

30

The reaction was concentrated *in vacuo*, acetone (200 mL) and an aqueous 5N solution of hydrogen chloride (100 mL) were added and the solution was heated at 40 °C for 2 h. The acetone was removed under reduced pressure and the aqueous layer was washed with dichloromethane (3 x 200 mL). The aqueous layer was then basified to pH 11 with aqueous solution of sodium hydroxide (1 N) and the product was extracted into dichloromethane (3 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford an orange solid. The solid was triturated with ethyl acetate to afford 3-iodo-1-(3-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine as a yellow solid (3.82 g, 25 %); RP-HPLC Rt 4.792 min, 92 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO) 1.54 (1H, m), 1.71 (1H, m), 2.01 (2H, m), 2.46 (1H, m), 2.81 (2H, m), 3.01 (1H, dd, *J* 11.8 and 3.4 Hz), 4.58 (1H, m), and 8.19 (1H, s).

15

B. 3-iodo-1-(1-methyl-3-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

To a mixture of 3-iodo-1-(3-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.4 g, 0.00116 mol) and sodium triacetoxyborohydride (0.34 g, 0.00162 mol) in dichloroethane (30 mL) was added formaldehyde solution (37 % in water, 0.035 mL, 0.00128 mol, 1.1 eq.) at room temperature. The mixture was stirred at room temperature under an atmosphere of nitrogen for 18 hours. Additional formaldehyde solution (37 % in water, 0.035 mL, 0.00128 mol, 1.1 eq.) was added, and the mixture was stirred at room temperature for 2 hours. A 5 N aqueous solution of sodium hydroxide (5 mL) was added to the mixture. The solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure, and the mixture was lyophilized to yield 3-iodo-1-(1-methyl-3-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.41 g, 0.0011 mol). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min,

30

1mL/min) Rt 6.0 min. MS: MH<sup>+</sup> 359

C. *N*2-{4-[4-amino-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

- 5 A mixture of 3-iodo-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.35 g, 0.001 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.44 g, 0.0012 mol), tetrakis(triphenylphosphine)-palladium (0.058 g, 0.00005 mol) and sodium carbonate (0.27 g, 0.0025 mol) in ethylene glycol dimethyl ether (30 mL) and water  
10 (6 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous  
15 sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 2 % - 10 % methanol / dichloromethane as a mobile phase to give *N*2-{4-[4-amino-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-  
20 2-amine (0.055 g, 0.00012 mol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  10.80 (s, 1H), 8.22 (s, 1H), 7.95 (d, 2H), 7.65 (d, 2H), 7.15 (s, 1H), 6.80 (s, 1H), 4.80 (br, 1H), 2.95 (br, 1H), 2.85 (br, 1H), 2.45 (br, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H), 2.00 (br, 3H), 1.80 (br, 1H), 1.70 (br, 1H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 10 min, 1mL/min) Rt  
25 9.7 min. MS: MH<sup>+</sup> 469

Example 603: *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

- 30 A. 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a mixture of 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

- (0.4 g, 0.00116 mol) and potassium carbonate (0.48 g, 0.00348 mol) in *N,N*-dimethylformamide (25 mL) were added 2-bromoethyl methyl ether (0.11 mL, 0.00116 mol) and potassium iodide (0.010 g, 0.000058 mol) at room temperature. The mixture was stirred at 65 °C under an atmosphere of nitrogen for 16 hours. The reaction mixture was cooled to room temperature, and additional 2-bromoethyl methyl ether (0.025 mL, 0.00027 mol) was added. The mixture was stirred at 65 °C under an atmosphere of nitrogen for 16 hours. The solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (4 x 50 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 $\mu$ m, 250 x 21.1 mm; 5% - 50% over 30 min with 0.1 M ammonium acetate, 21 mL/min) to 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.2 g, 0.0005 mol). TLC (methanol / dichloromethane = 10 : 90)  $R_f$  0.5 MS:  $MH^+$  403

B. *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

- The mixture of 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.16 g, 0.0004 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amine (0.17 g, 0.00048 mol), tetrakis(triphenylphosphine)palladium (0.023 g, 0.00002 mol) and sodium carbonate (0.11 g, 0.001 mol) in ethylene glycol dimethyl ether (25 mL) and water (5 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 2% - 10% methanol / dichloromethane as a mobile phase to give *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-

3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.17 g, 0.00033 mol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  10.85 (s, 1H), 8.22 (s, 1H), 7.95 (d, 2H), 7.65 (d, 2H), 7.14 (s, 1H), 6.80 (s, 1H), 4.79 (br, 1H), 3.50 (m, 2H), 3.25 (s, 3H), 3.10 (br, 1H), 2.90 (br, 1H), 2.55 (br, 2H), 2.54 (br, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.05 (br, 3H), 1.80 (br, 1H), 1.70 (br, 1H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1 mL/min) Rt 9.9 min. MS: MH<sup>+</sup> 513

Example 604: *N*2-{4-[4-amino-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine acetate

A. *tert*-Butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate

Di-*tert*-butyl dicarbonate (2.093 g, 0.00959 mol) was added to a solution of 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine (3.00 g, 0.00872 mol) and sodium carbonate (3.23 g, 0.0305 mol) in 1,4-dioxane (50 mL) and water (50 mL). The mixture was stirred at room temperature for 2 h and the resulting white precipitate was collected by filtration. The solid was washed with water (10 mL) and dried in air to afford *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate as a white solid (3.40 g, 88 %); RP-HPLC Rt 12.532 min, 98 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1 mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO) 1.34 (9H, br s), 1.50 (2H, m), 2.02 (1H, m), 2.13 (1H, m), 2.97 (2H, m), 3.85 (2H, m), 4.59 (1H, m), and 8.21 (1H, s).

25

B. *tert*-Butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate

The mixture of *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (0.6 g, 0.00135 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.59 g, 0.00162 mol), tetrakis(triphenylphosphine)palladium (0.078 g, 0.000068 mol) and sodium

30



- carbonate (0.36 g, 0.00338 mol) in ethylene glycol dimethyl ether (50 mL) and water (10 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. After cooled the mixture to the room temperature, more *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.24 g, 0.00066 mol), tetrakis(triphenylphosphine)palladium (0.078 g, 0.000068 mol) were added, and the mixture was stirred at 80 °C for 5 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish oil which was purified by flash column chromatography on silica using 5 % - 25 % isopropanol / dichloromethane as a mobile phase, and the product was triturated with *N,N*-dimethylformamide to give *tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (0.28 g, 0.00051 mol). RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.9 min.
- 20 MS: MH<sup>+</sup> 555

C. *N*2-{4-[4-amino-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine acetate

- To a mixture of *tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (0.28 g, 0.00051 mol) in acetone (10 mL) was added an 6*N* aqueous solution of hydrogen chloride (3 mL) at room temperature. The mixture was stirred at 45 °C for 1 hour. The solvent was removed, and the mixture was basified with an aqueous 5*N* sodium hydroxide solution. The aqueous layer was extracted with dichloromethane (3 x 80 mL). The solvent was removed under reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8µm, 250 x 21.1 mm; 5% - 100% over 20 min with 0.1 M ammonium acetate, 21mL/min) to yield *N*2-{4-[4-amino-1-(3-piperidyl)-

1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine acetate (0.06 g, 0.00012 mol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  10.85 (s, 1H), 8.22 (s, 1H), 7.95 (d, 2H), 7.65 (d, 2H), 7.05 (s, 1H), 6.80 (s, 1H), 4.75 (br, 1H), 3.15 (br, 2H), 2.95 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 2.05 (br, 1H), 2.00 (br, 1H), 1.90 (s, 3H), 1.80 (br, 1H), 1.60 (br, 1H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.4 min. MS: MH<sup>+</sup> 455

Example 605: 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-(dimethylamino)-1-ethanone acetate

A mixture of *N*2-[4-[4-amino-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine acetate (0.04 g, 0.000078 mol), dimethylglycine (0.01 g, 0.000097 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.019 g, 0.000097mol), *N,N*-diisopropylethylamine (0.033g, 0.00026 mol) and 1-hydroxy-7-azabenzotriazole (0.011 g, 0.000078 mol) in anhydrous dichloromethane (5 mL) was stirred for 18 hours at room temperature. The solvent was removed under reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane, and the combined organic solvent was washed with brine. The solvent was removed under reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8 $\mu$ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-(dimethylamino)-1-ethanone acetate (0.015 g, 0.00003 mol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  10.85 (s, 1H), 8.27 (d, 1H), 7.94 (d, 2H), 7.67 (d, 2H), 7.11 (s, 1H), 6.51 (s, 1H), 4.81 – 1.91 (br, 11 H), 2.40 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H), 1.91 (s, 3H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.7 min. MS: MH<sup>+</sup> 540

Example 606: 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-methyl-2-(methylamino)-1-propanone

- 5           A.     3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride

To a mixture of *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (1.2 g, 0.0027 mol) in acetone (20 mL) was added an aqueous 6*N* solution of hydrogen chloride (8 mL) at room temperature. The mixture was stirred at 45 °C for 1.5 hours, and then room temperature for 16 hours. The precipitate was filtered and washed with acetone. The solid was dried to give 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (1 g, 0.0024 mol). TLC (methanol / dichloromethane = 5 : 95) *R*<sub>f</sub> 0.14 MS: MH<sup>+</sup> 345

- 15           B.     9*H*-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate

A mixture of 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (0.17 g, 0.00042 mol), 2-[(9*H*-9-fluorenylmethoxy)carbonyl]-(methylamino)-2-methylpropanoic acid (0.175 g, 0.00052 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.1 g, 0.00052 mol), *N,N*-diisopropylethylamine (0.23 g, 0.0018 mol) and 1-hydroxy-7-azabenzotriazole (0.057 g, 0.00042 mol) in anhydrous dichloromethane (7 mL) was stirred for 18 hours at room temperature. Additional 2-[(9*H*-9-fluorenylmethoxy)carbonyl]-(methylamino)-2-methylpropanoic acid (0.044 g, 0.00013 mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.025 g, 0.00013 mol) were added to the reaction and stirred for 16 hours. The solvent was removed under reduced pressure. The residue was partitioned between brine and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic solvent was removed under reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8μm, 250 x 21.1 mm; 5% - 100% over 20 min with 0.1 M ammonium acetate, 21mL/min) to yield 9*H*-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate (0.030g, 0.00005 mol). RP-HPLC (Delta Pak C18,

5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.2 min. MS: MH<sup>+</sup> 666

C. 9H-9-fluorenylmethyl *N*-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl})-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl-*N*-methylcarbamate

A mixture of 9H-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate (0.03 g, 0.000045 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.02 g, 0.000054 mol), tetrakis(triphenylphosphine)-palladium (0.003 g, 0.000002 mol) and sodium carbonate (0.0126 g, 0.00011 mol) in ethylene glycol dimethyl ether (4 mL) and water (1 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid, which was carried to the next reaction. RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.4 min. TLC (methanol / dichloromethane = 5 : 95) R<sub>f</sub> 0.80

D. 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl})-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-methyl-2-(methylamino)-1-propanone

A crude mixture of 9H-9-fluorenylmethyl *N*-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl})-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl-*N*-methylcarbamate (0.037 g, 0.00005 mol) in a 25 % solution of piperidine in *N,N*-dimethylformamide (10 mL) was stirred for 16 hours at room temperature under an atmosphere of nitrogen. The solvent was removed, and the residue was partitioned between ethyl acetate and water. The

combined organic layer was washed with brine and dried over magnesium sulfate. The solvent was removed, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8 $\mu$ m, 250 x 21.1 mm; 5% - 100% over 30 min with 0.1 M ammonium acetate, 21 mL/min) to yield 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-methyl-2-(methylamino)-1-propanone (0.011 g, 0.00002 mol). <sup>1</sup>H NMR (Chloroform-*d*, 400 MHz)  $\delta$  8.35 (s, 1H), 7.75 (m, 2H), 7.40 (m, 2H), 7.10 (s, 1H), 6.78 (s, 1H), 4.98 – 1.70 (br, 9 H), 2.49 (s, 3H), 2.48 (s, 3H), 2.40 (s, 3H), 2.10 (s, 6H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1 mL/min) Rt 10.0 min. MS: MH<sup>+</sup> 554

Example 607: *N*2-4-[4-amino-1-(3-azetanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-5,7-dimethyl-1,3-benzoxazol-2-amine

A. *tert*-Butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetanecarboxylate

A mixture of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.73 g, 0.0028 mol), *tert*-butyl 3-[(methylsulfonyl)oxy]-1-azetanecarboxylate (1.05 g, 0.0042 mol) and cesium carbonate (1.4 g, 0.0042 mol) in *N,N*-dimethylformamide (25 mL) were stirred at 70 °C under an atmosphere of nitrogen for 16 hours. The mixture was cooled to room temperature. Additional *tert*-butyl 3-[(methylsulfonyl)oxy]-1-azetanecarboxylate (0.35 g, 0.0014 mol) and cesium carbonate (0.46 g, 0.0014 mol) were added to the mixture. The mixture was stirred at 70 °C under an atmosphere of nitrogen for 16 hours. The solvent was removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with dichloromethane (3 x 70 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure. The residue was triturated with dichloromethane (2 x 3 mL) to give *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetanecarboxylate (0.57 g, 0.0014 mol). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1 mL/min) Rt 9.4 min. MS: MH<sup>+</sup> 417

B. *tert*-Butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetancarboxylate

A mixture of *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetancarboxylate (0.15 g, 0.00036 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.16 g, 0.00045 mol), tetrakis(triphenylphosphine)palladium (0.021 g, 0.000018 mol) and sodium carbonate (0.095 g, 0.0009 mol) in ethylene glycol dimethyl ether (5 mL) and water (2 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The reaction was cooled to room temperature. Additional tetrakis(triphenylphosphine)palladium (0.021 g, 0.000018 mol) was added to the mixture. The reaction was stirred at 80 °C for 3 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 5 % - 50 % methanol / dichloromethane as a mobile phase to give *tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetancarboxylate (0.033 g, 0.00006 mol). RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.6 min. MS: MH<sup>+</sup> 527

C. *N*2-4-[4-amino-1-(3-azetanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-5,7-dimethyl-1,3-benzoxazol-2-amine

To a mixture of *tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetancarboxylate (0.033 g, 0.000063 mol) in acetone (4 mL) was added an aqueous 6*N* solution of hydrogen chloride (0.3 mL) at room temperature. The mixture was stirred at 45 °C for 2 hour, and then at room temperature for 16 hours. The solid from the reaction

was filtered and washed with acetone. In order to remove some impurities, the solid was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with brine. The solvent was removed to yield N2-4-[4-amino-1-(3-azetanyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl-5,7-dimethyl-1,3-benzoxazol-2-amine (0.004 g, 0.00001 mol).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  10.85 (s, 1H), 8.45 (s, 1H), 8.00 (d, 2H), 7.75 (d, 2H), 7.09 (s, 1H), 6.80 (s, 1H), 5.90 (br, 1H), 5.20 (m, 4H), 2.40 (s, 3H), 2.20 (s, 3H).  
RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 10 min, 1 mL/min) Rt 9.1 min. MS: MH<sup>+</sup> 427

Example 608: N2-{4-[4-amino-1-(1-methyl-3-azetanyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

A. 1-(3-azetanyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine diacetate

A mixture of *tert*-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-azetane-1-carboxylate (0.41 g, 0.00099 mol) in acetone (5 mL) was added to an aqueous 6N solution of hydrogen chloride (1 mL) at room temperature. The mixture was stirred at 45 °C for 2 hours. The solvent was removed under reduced pressure, and the residue was basified with an aqueous 5N solution of sodium hydroxide at 0 °C. The aqueous layer was extracted with dichloromethane (3 x 50 mL), and the organic layer was washed with brine and dried under magnesium sulfate. The solvent was removed under reduced pressure. The aqueous layer and the residue from organic layer were combined. The solvents were removed, and the residue was suspended in *N,N*-dimethylformamide, methanol, and acetic acid and purified by RP-HPLC (Hypersilprep HS C18, 8 $\mu$ m, 250 x 21.1 mm; 5% - 100% over 30 min with 0.1 M ammonium acetate, 21 mL/min) to 1-(3-azetanyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine diacetate (0.165 g, 0.0005 mol).  
TLC (methanol/dichloromethane 5:95) R<sub>f</sub> 0.29. MS: MH<sup>+</sup> 317

B. 3-iodo-1-(1-methyl-3-azetanyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

To a mixture of 1-(3-azetanyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-

amine diacetate (0.165 g, 0.0005 mol) and sodium triacetoxymethylborohydride (0.15 g, 0.00073 mol) in dichloroethane (15 mL) was added a 37% solution of formaldehyde in 0.016 mL, 0.000572 mol) at room temperature. The mixture was stirred at room temperature under an atmosphere of nitrogen for 16 hours. Additional formaldehyde (37 % in water, 0.016 mL, 0.000572 mol) and sodium triacetoxymethylborohydride (0.15 g, 0.00073 mol) were added, and the mixture was stirred at room temperature for 2 days. An aqueous 5N solution of sodium hydroxide (1 mL) was added to the mixture. The solvent was removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure. Majority product was still in aqueous layer. The aqueous layer and the residue from organic layer were combined. The solvent was removed, and the residue was carried to the next step without purification. TLC (methanol / dichloromethane = 10 : 90)  $R_f$  0.48 MS:  $MH^+$  331

C. *N*2-{4-[4-amino-1-(1-methyl-3-azetanyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

A mixture of 3-iodo-1-(1-methyl-3-azetanyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.17 g, 0.00052 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.23 g, 0.000624 mol), tetrakis(triphenylphosphine)-palladium (0.030 g, 0.000026 mol) and sodium carbonate (0.14 g, 0.0013 mol) in ethylene glycol dimethyl ether (20 mL) and water (15 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The reaction was cooled to room temperature. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 5 % - 50 % methanol / dichloromethane as a mobile phase to give *N*2-{4-[4-amino-1-(1-methyl-3-azetanyl)-1H-pyrazolo[3,4-



*d*]pyrimidin-3-yl]phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.13 g, 0.0003 mol).

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  10.85 (s, 1H), 8.15 (s, 1H), 7.90(d, 2H), 7.70 (d, 2H), 7.09(s, 1H), 6.85(s, 1H), 5.40 (br, 1H), 3.90 (m, 2H), 3.70 (m, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.5 min. MS: MH<sup>+</sup> 441

- Example 609: *Cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carbonitrile

A. 3-amino-4-hydroxybenzonitrile

- To a mixture of 4-hydroxy-3-nitrobenzonitrile (4 g, 0.0244 mol) in ethanol (180 mL) and water (90 mL) was added sodium thiosulfate (17 g, 0.0976 mol) at room temperature. The heterogeneous mixture was stirred at 80 °C under an atmosphere of nitrogen for 1 hour. The reaction mixture was cooled to room temperature, and ethanol was removed under reduced pressure. The yellow solid was filtered, washed with water, and dried under reduced pressure to yield 3-amino-4-hydroxybenzonitrile (1.46 g, 0.011 mol).
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 4.5 min. MS: MH<sup>+</sup> 133

B. 2-(4-bromoanilino)-1,3-benzoxazole-5-carbonitrile

- To a mixture of 3-amino-4-hydroxybenzonitrile (1.84 g, 0.0137 mol) in acetonitrile (140 mL) was added 4-bromophenyl isothiocyanate (2.93 g, 0.0137 mol) at room temperature. The mixture was stirred for 16 hours at room temperature. Cuprous chloride (1.36 g, 0.0137 mol) and triethylamine (1.9 mL, 0.0137 mol) were added to the reaction mixture. The mixture was stirred for 16 hours at room temperature. The solvent was removed under reduced pressure, and the solid was suspended in methanol. The mixture was filtered through celite pad using methanol. The brownish filtrate was left at 4° for three days. The precipitate was filtered and washed with methanol to yield 2-(4-bromoanilino)-1,3-benzoxazole-5-carbonitrile

(2.4 g, 0.0076 mol). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.1 min. MS: MH<sup>+</sup>: 313

- 5 C. 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1,3-benzoxazole-5-carbonitrile

A mixture of 2-(4-bromoanilino)-1,3-benzoxazole-5-carbonitrile (1.8 g, 0.0058mol), diboron pinacol ester (1.8 g, 0.007 mol), [1.1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with  
10 dichloromethane (1:1) (0.47g, 0.00058 mol) and potassium acetate (1.7 g, 0.0174 mol) in *N,N*-dimethylformamide (50 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica using 0 % - 40 % ethyl acetate / n-heptane as a  
15 mobile phase to give 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1,3-benzoxazole-5-carbonitrile (0.80 g, 0.0022 mol). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) Rt 16.9 min. MS: MH<sup>+</sup>: 362

- 20 D. *cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carbonitrile

A mixture of 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.15 g, 0.00034 mol), 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1,3-benzoxazole-5-carbonitrile (0.153 g, 0.000425 mol),  
25 tetrakis(triphenylphosphine)palladium (0.028 g, 0.0000238 mol) and sodium carbonate (0.090g, 0.00085 mol) in ethylene glycol dimethyl ether (3 mL) and water (1 mL) was heated at 80°C for 16 hours. Additional 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1,3-benzoxazole-5-carbonitrile (0.072g, 0.0002 mol),  
30 tetrakis(triphenylphosphine)palladium (0.012 g, 0.000010 mol, 0.03 eq.) were added, and the mixture was stirred at 80 °C for 16 hours under atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was

removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure, and the residue was purified by flash column chromatography on silica using 2 % aqueous ammonium hydroxide solution / 5 % - 20 % methanol / dichloromethane as a mobile phase. The solvent was removed under reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8 $\mu$ m, 250 x 21.1 mm; 5% - 50% over 30 min with 0.1 M ammonium acetate, 21mL/min) to give *cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carbonitrile (0.15g, 0.00027 mol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  11.25 (s, 1H), 8.53 (s, 1H), 8.00 (s, 1H), 7.95 (d, 2H), 7.70(m, 4H), 4.80 (br, 1H), 2.49 (s, 3H), 2.20 (br, 8H), 2.10 (br, 3H), 1.75 (br, 2H), 1.60 (br, 4H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.2 min. MS: MH<sup>+</sup> 549.

Example 610: *Cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine

A. 2-nitro-4-(trifluoromethoxy)phenol

To a mixture of 4-(trifluoromethoxy)phenol (4 g, 0.0225mol) in ethylene glycol dimethyl ether (90 mL) was added a 0.5 M solution of nitronium tetrafluoroborate in sulfolane ( 46 mL, 0.0229 mol) at -50 °C. The mixture was stirred at -50 °C under an atmosphere of nitrogen for 6 hours. The mixture was filtered through silica gel pad, and the pad was washed with 25 % ethyl acetate / n-heptane. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with water and brine. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica using 0 % - 50 % ethyl acetate / n-heptane as a mobile phase to give 2-nitro-4-(trifluoromethoxy)phenol (2.5 g, 0.011 mol). TLC (ethyl

acetate / n-heptane = 25 : 75)  $R_f$  0.50 MS: MH<sup>+</sup>: 222

B. 2-amino-4-(trifluoromethoxy)phenol

To a mixture of 2-nitro-4-(trifluoromethoxy)phenol (2 g, 0.0089 mol) in ethanol (50 mL) and water (25 mL) was added sodium thiosulfate (6.2 g, 0.0356 mol) at room temperature. The heterogeneous mixture was stirred at 80 °C under an atmosphere of nitrogen for 1 hour. The reaction mixture was cooled to room temperature, and ethanol was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 x 70 mL), and the organic layer was washed with brine and dried under sodium sulfate. The solvent was removed under reduced pressure to give yellow solid of 2-amino-4-(trifluoromethoxy)phenol (0.9 g, 0.005 mol). TLC (methanol / dichloromethane = 5 : 95)  $R_f$  0.29 MS: MH<sup>+</sup>: 194

C. N2-(4-bromophenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine

To a mixture of 2-amino-4-(trifluoromethoxy)phenol (0.9 g, 0.0047 mol) in tetrahydrofuran (60 mL) was added 4-bromophenyl isothiocyanate (1 g, 0.0047 mol) at room temperature. The mixture was stirred for 16 hours at room temperature. Anhydrous copper sulfate (7.1 g, 0.0443 mol, 9.43 eq.), triethylamine (0.67 mL, 0.0047 mol, 1 eq.), and silica gel (8.5 g) were added to the reaction mixture. The mixture was stirred for 4 hours at room temperature. The solvent was removed under reduced pressure. The mixture was filtered through silica gel pad using 25 % ethyl acetate / n-heptane as a mobile phase to give orange colored solid. The solid was purified by flash column chromatography on silica using 0 % - 25 % ethyl acetate / n-heptane as a mobile phase. The solvent was removed, and the residue was triturated with n-heptane to give N2-(4-bromophenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.9 g, 0.0024 mol).

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min)  $R_t$  12.2 min. MS: MH<sup>+</sup>: 373

D. N2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine

A mixture of N2-(4-bromophenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.9 g, 0.0024 mol), diboron pinacol ester (0.73 g, 0.0029 mol), [1.1'-

bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1:1) (0.2 g, 0.00024 mol) and potassium acetate (0.71 g, 0.0072 mol) in *N,N*-dimethylformamide (25 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. The residue was filtered through silica pad 25 % ethyl acetate / n-heptane as a mobile phase. The solvent was removed, and the residue was triturated with n-heptane to give *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.68 g, 0.0016 mol). RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) Rt 18.8 min. MS: MH<sup>+</sup>: 421

E. *cis-N*2-(4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazol[3,4-*d*]pyrimidin-3-yl]phenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine

A mixture of 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazol[3,4-*d*]pyrimidin-4-amine (0.06g, 0.00014 mol), *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.071 g, 0.00017 mol), tetrakis(triphenylphosphine)palladium (0.011 g, 0.00001 mol) and sodium carbonate (0.037, 0.00035 mol) in ethylene glycol dimethyl ether (3 mL) and water (1 mL) was heated at 80°C for 16 hours. Additional *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.030 g, 0.00007 mol) and tetrakis(triphenylphosphine)palladium (0.005 g, 0.000004 mol) were added, and the mixture was stirred at 80 °C for 5 hours under atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure, and the residue was purified by flash column chromatography on silica using 2 % aqueous ammonium hydroxide solution / 5 % - 25 % methanol / dichloromethane as a mobile phase. The solvent was removed under reduced pressure to give *cis-N*2-(4-

{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.065 g, 0.00011 mol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  11.25 (s, 1H), 8.20 (s, 1H), 7.95 (d, 2H), 7.65 (m, 3H), 7.50 (s, 1H), 7.15 (s, 1H), 4.80 (br, 1H), 2.60 (br, 9H), 2.49 (s, 3H), 2.20 (br, 3H), 2.10 (br, 1H), 1.75 (br, 2H), 1.60 (br, 2H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.7 min. MS: MH<sup>+</sup> 608

Example 611: *Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine

A. 4-ethyl-2-nitrophenol

To a mixture of 4-ethylphenol (4 g, 0.0328mol) in ethylene glycol dimethyl ether (100 mL) was added a 0.5 M solution of nitronium tetrafluoroborate in sulfolane (67 mL, 0.0335 mol) at –50 °C. The mixture was stirred at –50 °C under the atmosphere of nitrogen for 6 hours. The mixture was filtered through silica gel pad, and the pad was washed with 25 % ethyl acetate / n-heptane. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with water and brine. The solvent was removed under reduced pressure to give about 10 g of crude 4-ethyl-2-nitrophenol. The crude material was used in the next step without purification.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  10.68 (s, 1H), 7.71 (s, 1H), 7.40 (d, 1H), 7.07 (d, 1H), 2.60 (q, 2H), 1.20 (t, 3H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.2 min.

B. 2-amino-4-ethylphenol

To a mixture of 4-ethyl-2-nitrophenol (5.5 g, 0.032 mol) in ethanol (180 mL) and water (90 mL) was added sodium thiosulfate (23 g, 0.131 mol) at room temperature. The heterogeneous mixture was stirred at 80 °C under an atmosphere of nitrogen for 16 hour. The reaction mixture was cooled to room temperature, and ethanol was removed under reduced pressure. The aqueous layer was extracted with

ethyl acetate (3 x 100 mL), and the organic layer was washed with brine and dried under sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica using 0 % - 25 % methanol / dichloromethane as a mobile phase (x 2). The solvent was removed under reduced pressure to give 2-amino-4-ethylphenol (0.89 g, 0.006 mol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  8.61 (br, 2H), 6.47 (d, 1H), 6.37 (s, 1H), 6.18 (d, 1H), 2.17 (q, 2H), 1.08 (t, 3H). MS: MH<sup>+</sup>: 137

C. *N*2-(4-bromophenyl)-5-ethyl-1,3-benzoxazol-2-amine

To a mixture of 2-amino-4-ethylphenol (0.89 g, 0.0065 mol) in tetrahydrofuran (80 mL) was added 4-bromophenyl isothiocyanate (1.4 g, 0.0065 mol) at room temperature. The mixture was stirred for 2 hours at room temperature. Anhydrous copper sulfate (6.2 g, 0.039 mol), triethylamine (0.9 mL, 0.0065 mol) and silica gel (11.7 g) were added to the reaction mixture. The mixture was stirred for 4 hours at room temperature. The solvent was removed under reduced pressure. The mixture was filtered through silica gel pad using 25 % ethyl acetate / *n*-heptane as a mobile phase to give brown colored solid. The solid was purified by flash column chromatography on silica using 0 % - 25 % ethyl acetate / *n*-heptane as a mobile phase. The solvent was removed, and the residue was triturated with *n*-heptane to give *N*2-(4-bromophenyl)-5-ethyl-1,3-benzoxazol-2-amine (0.96 g, 0.003 mol). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 12.1 min. MS: MH<sup>+</sup>: 318

D. *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-ethyl-1,3-benzoxazol-2-amine

A mixture of *N*2-(4-bromophenyl)-5-ethyl-1,3-benzoxazol-2-amine (0.86 g, 0.0027 mol), diboron pinacol ester (0.84 g, 0.0033 mol), [1.1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1:1) (0.22 g, 0.0027 mol) and potassium acetate (0.8 g, 0.0081 mol) in *N,N*-dimethylformamide (30 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature

and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the organic layer was washed with brine. The solvent was removed under reduced pressure, and the crude material was purified by flash column

- 5 chromatography on silica using 0 % - 25 % ethyl acetate / n-heptane as a mobile phase to give *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-ethyl-1,3-benzoxazol-2-amine (0.82 g, 0.002 mol).

TLC (ethyl acetate / n-heptane = 25 : 75)  $R_f$  0.30. MS:  $MH^+$ : 365

- 10 E. *cis*- *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine

- A mixture of 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.06g, 0.00014 mol), *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-ethyl-1,3-benzoxazol-2-amine (0.062 g, 0.00017 mol),  
15 tetrakis(triphenylphosphine)palladium (0.011 g, 0.00001 mol) and sodium carbonate (0.037, 0.00035 mol) in ethylene glycol dimethyl ether (3 mL) and water (1 mL) was heated at 80°C for 16 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue  
20 was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure, and the residue was purified by flash column chromatography on silica using 2 %  
25 aqueous ammonium hydroxide solution / 5 % - 25 % methanol / dichloromethane as a mobile phase. The solvent was removed under reduced pressure to give *cis*- *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine (0.065g, 0.00012 mol).  $^1H$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  11.25 (s, 1H), 8.65 (s, 1H), 8.37 (d, 2H), 8.09 (d, 2H), 7.84  
30 (d, 1H), 7.76 (s, 1H), 7.42 (d, 1H), 5.22 (br, 1H), 3.13 (q, 2H), 2.52 (br, 7H), 2.69 (br, 4H), 2.64 (s, 3H), 2.49 (br, 2H), 2.11 (br, 2H), 2.01 (br, 2H), 1.63 (t, 3H). RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium



acetate over 10 min, 1mL/min) Rt 10.3 min. MS: MH<sup>+</sup> 552

Examples 612: *Cis-N*2-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine; and

Example 613: *Cis-N*2-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A. *Cis*- and *trans*-1-[4-(dimethylamino)cyclohexyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Sodium triacetoxymethylborohydride (1.40 g, 6.61 mmol) was added to a solution of 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-cyclohexanone monohydrochloride (2.00 g, 5.08 mmol), dimethylamine solution (2 M in tetrahydrofuran, 7.62 mL, 15.24 mmol) and acetic acid (0.87 mL, 15.24 mmol) in 1,2-dichloroethane (200 mL) at room temperature. The reaction was stirred for 24 h and additional sodium triacetoxymethylborohydride (0.40g) was added. After a further 24h, saturated aqueous NaHCO<sub>3</sub> (50 mL) and CH<sub>2</sub>Cl<sub>2</sub> (200 mL) were added and the organic layer was separated, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The product was purified by column chromatography using a 1:5:94 aqueous ammonium hydroxide : MeOH : CH<sub>2</sub>Cl<sub>2</sub> to 1 : 20 : 79 94 aqueous ammonium hydroxide : MeOH : CH<sub>2</sub>Cl<sub>2</sub> gradient as the eluent to afford a mixture of *cis*- and *trans*-1-[4-(dimethylamino)cyclohexyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a white crystalline solid (0.87 g, 44 %); RP-HPLC Rt 5.458 min, 33 % purity, *trans*-isomer; Rt 5.621 min, 67 % purity, *cis*-isomer (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 387 (MH<sup>+</sup>) was observed for both the *cis*- and the *trans*-isomers.

B. *Cis*- and *trans-N*2-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A mixture of *cis*- and *trans*-1-[4-(dimethylamino)cyclohexyl]-3-iodo-1H-

- pyrazolo[3,4-d]pyrimidin-4-amine (0.50 g, 1.29 mmol), *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.565 g, 1.55 mmol), sodium carbonate (0.34 g, 3.24 mmol), and *tetrakis*(triphenylphosphine) palladium (0) (0.075 g, 0.06 mmol) in ethylene glycol dimethylether (150 mL) and water (25 mL) was heated at 80 °C for 16 h. Additional Pd catalyst (0.075 g) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.40 g) were added and the reaction was continued at 80 °C for a further 16 h. Further quantities of the Pd catalyst (0.020 g) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.12 g) were added and the reaction was continued at 80 °C for a further 16 h. The reaction was concentrated *in vacuo* and the residues were dissolved in dichloromethane (200 mL) and washed with water (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using 1 % aqueous ammonium hydroxide and 10% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford *cis*-*N*2-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.08 g), a mixed fraction (0.24 g) and *trans*-*N*2-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.030 g); RP-HPLC Rt 11.326 min, 100 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 497 (MH<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO) 1.49 (2H, *m*), 2.01 (6H, *m*), 2.33 (7H, *m*), 2.35 (3H, *s*), 2.40 (3H, *s*), 4.67 (1H, *m*), 6.80 (1H, *s*), 7.11 (1H, *s*), 7.65 (2H, *d*, *J* 8.5 Hz), 7.92 (2H, *d*, *J* 8.5 Hz), 8.23 (1H, *s*), and 10.85 (1H, *s*).
- The *cis*-fraction required further purification by RP HPLC to afford *cis*-*N*2-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.050 g), RP-HPLC Rt 11.337 min, 100 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO) 1.61 (4H, *m*), 2.08 (2H, *m*), 2.27 (9H, *m*), 2.34 (3H, *s*), 2.40 (3H, *s*), 4.81 (1H, *m*), 6.80 (1H, *s*), 7.11 (1H, *s*), 7.65 (2H, *d*, *J*

8.5 Hz), 7.92 (2H, *d*, *J* 8.5 Hz), 8.23 (1H, *s*), and 10.85 (1H, *s*).

#### Exempls 614-620

- 5       The following is a general synthesis of analogs of *cis*-*N*2-4-[4-amino-1-(4-aminocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-1,3-benzoxazol-2-amine. Examples 614-620 were prepared using this method.

#### A.   *N*2-(4-Bromophenyl)-5-chloro-1,3-benzoxazol-2-amine

- 10       4-Bromophenyl isothiocyanate (3.639 g, 17.00 mmol) was added to a solution of 2-amino-4-chlorophenol (2.441 g, 17.00 mmol) in acetonitrile (20 mL) and the reaction was stirred at room temperature for 2 h. The resulting brown solution was then added dropwise, via a dropping funnel, to a suspension of potassium superoxide (6.04 g, 85.0 mmol) in acetonitrile (20 mL) pre-cooled to 0 °C
- 15       in an ice bath. After 20 minutes the initial exotherm had subsided and the reaction was allowed to warm to room temperature for 40 minutes. Water (120 mL) was added dropwise and the resulting off-white solid was collected by filtration, washed with additional water (60 mL) and dried overnight on a lyophilizer to afford *N*2-(4-bromophenyl)-5-chloro-1,3-benzoxazol-2-amine as an off-white solid (4.06 g, 74 %);
- 20       RP-HPLC Rt 17.229 min, 99 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1 mL/min;  $\lambda = 254$  nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); *m/z* 321 (M-H)<sup>+</sup> and 323 (M-H)<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO) 7.17 (1H, *dd*, *J* 8.5 and 1.9 Hz), 7.53 (4H, *m*), 7.71 (2H, *d*, *J* 8.8 Hz), and 10.95 (1H, *s*).

- 25       B.   *N*2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-chloro-1,3-benzoxazol-2-amine

- A mixture containing *N*2-(4-bromophenyl)-5-chloro-1,3-benzoxazol-2-amine (4.00 g, 12.36 mmol), *bis*(pinacolato)diboron (3.77 g, 14.83 mmol), potassium acetate (3.64 g, 37.09 mmol) and [1,1'-*bis*(diphenylphosphino)ferrocene]dichloropalladium (II) complexed with dichloromethane (1 : 1) (0.61 g, 0.74 mmol) in dimethylformamide (200 mL) was heated at 80 °C under nitrogen for 16 h. Additional Pd catalyst (0.61 g) was added
- 30

and the reaction was continued for a further 6 h. Additional diboron (3.0 g) was then added and the reaction proceeded for a further 16 h. Silica gel (20 mL) was added to the reaction mixture and the solvent removed under reduced pressure. The resulting solid was then purified through a silica pad using a 10% to 20% ethyl acetate in heptane gradient as the eluent. The resulting solid was triturated with heptane to afford N2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-chloro-1,3-benzoxazol-2-amine as a cream solid (2.40 g, 52 %); RP-HPLC Rt 18.164 min, 99 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO) 1.29 (12H, s), 7.17 (1H, dd,  $J$  8.5 and 2.1 Hz), 7.56 (2H, m), 7.68 (2H, m), 7.75 (2H, m), and 10.96 (1H, s).

C. N2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine

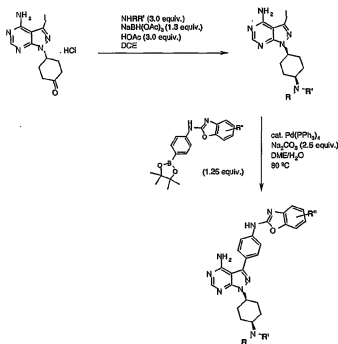
2-Amino-4-methylphenol (1.15 g, 9.34 mmol) was added to a solution of 4-bromophenyl isothiocyanate (2.00 g, 9.34 mmol) in tetrahydrofuran (35 mL) and the reaction was stirred at room temperature for 16 h. Anhydrous copper (II) sulfate (14.06 g, 88.10 mmol), silica gel (14.06 g), and triethylamine (1.3 mL, 9.34 mmol) were added, and the mixture was stirred at room temperature for 24 h. The reaction was concentrated under reduced pressure and then added to a silica pad and purified using 1 : 5 ethyl acetate : heptane (2 L) followed by diethyl ether as the eluent to afford N2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine as a light brown solid (2.30 g, 81 %); RP-HPLC Rt 16.437 min, 94% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO) 2.37 (3H, s), 6.94 (1H, d,  $J$  8.1 Hz), 7.27 (1H, s), 7.36 (1H, d,  $J$  8.1 Hz), 7.54 (2H, d,  $J$  8.4 Hz), 7.72 (2H, d,  $J$  8.4 Hz), and 10.72 (1H, s).

D. N2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-methyl-1,3-benzoxazol-2-amine

N2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-methyl-1,3-benzoxazol-2-amine was prepared from N2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine (1.5 g, 4.95 mmol) using the method described for the preparation of N2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-chloro-

- 1,3-benzoxazol-2-amine. The product was formed as white flocculent solid (0.79 g, 46 %); RP-HPLC Rt 17.382 min, 98% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda = 254$  nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO) 1.29 (12 H, s), 2.38 (3H, s), 6.94 (1H, d,  $J$  8.1 Hz), 7.30 (1H, s), 7.36 (1H, d,  $J$  8.1 Hz), 7.67 (2H, d,  $J$  8.5 Hz), 7.75 (2H, d,  $J$  8.5 Hz), and 10.74 (1H, s).

E. General synthesis of cyclohexyl amine analogs of cis-1-(4-aminocyclohexyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine



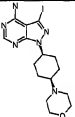

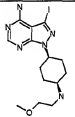

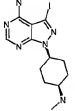

10

- 4-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanone monohydrochloride (5.08-7.62 mmol scale) was suspended in dichloroethane (200-300 mL) under a nitrogen atmosphere. The appropriate amine (3.0 equivalents), glacial acetic acid (3.0 equivalents) and sodium triacetoxyborohydride (1.3 equivalents) were added and the reaction was stirred at ambient temperature for 1-2 days. For the reactions which had not gone to completion, additional sodium triacetoxyborohydride (1.3 equivalents) was added and the reaction was continued

for a further 1 or 2 days. The reactions were quenched with saturated sodium carbonate solution (50-75 mL) and extracted with dichloromethane (200-300 mL). The organic phase was separated, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to yield a mixture of *cis*- and *trans*-products as a white solid. The crude

- 5 products were purified via flash column chromatography using a gradient of 2% methanol and 0.2% ammonium hydroxide in dichloromethane to 5% methanol and 0.5% ammonium hydroxide in dichloromethane as the eluent. The fractions containing the pure *cis*-products were combined, concentrated under reduced pressure and dried on a lyophilizer to afford the cyclohexyl amine analogs of *cis*-1-  
10 (4-aminocyclohexyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as white solids (see Table 1 for analytical details and isolated yields).

Table 1

Structure	Starting amine	Starting cyclohexanone scale (mmol)	<i>m/z</i> (MH <sup>+</sup> )	HPLC RT (min)	Purity	% Isolated yield of <i>cis</i> -isomer
		5.08	429.0	5.63	95%	8
		7.62	417.0	5.96	100%	59
		7.62	373.0	5.32	100%	2

RP-HPLC analysis conditions: 5% to 85% acetonitrile/0.1M aqueous ammonium

acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda = 254$  nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column.

F. General synthesis of analogs of *cis*-N2-4-[4-amino-1-(4-aminocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-1,3-benzoxazol-2-amine

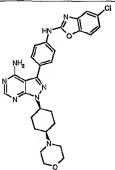
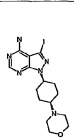
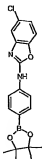
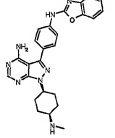
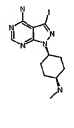
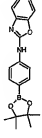
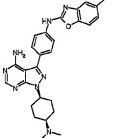
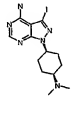
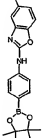
The cyclohexylamine analog of *cis*-1-(4-aminocyclohexyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.10-0.52 mmol scale) was dissolved in ethylene glycol dimethylether (5-10 mL) and water (2.5-5 mL). The appropriate substituted or unsubstituted *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (1.25 equivalents), *tetrakis*(triphenylphosphine) palladium (0) (0.05 equivalents) and sodium carbonate (2.5 equivalents) were added and the reaction was heated at 80 °C for 20 hours. For the reactions which had not reached completion, additional boronate (1.25 equivalents) and palladium catalyst (0.05 equivalents) were added. In addition, DME/H<sub>2</sub>O 2:1 (5 mL) was added to the reactions where precipitation had occurred and the reactions were re-subjected to heating at 80 °C for a further 22-40 hours. Silica gel (5-8 mL) was added to the reaction and the mixture was concentrated under reduced pressure. Purification via flash column chromatography over silica gel using a gradient of 2% to 50% methanol containing 0.5M ammonium hydroxide in dichloromethane yielded analogs of *cis*-N2-4-[4-amino-1-(4-aminocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-1,3-benzoxazol-2-amine. For products with unsatisfactory purity, the samples were further purified via RP-HPLC (Waters PrepLC 4000, flow rate: 10 mL/min,  $\lambda = 254$  nm, gradient: 15% to 35% acetonitrile/0.1M aqueous ammonium acetate gradient over 40 minutes then 35% to 90% acetonitrile/0.1M aqueous ammonium acetate gradient over 150 minutes; Deltapak C18, 300Å, 15  $\mu$ m, 40 x 100 mm column). The fractions containing the desired products were combined and concentrated *in vacuo* then dried on a lyophilizer to afford the products as white or tan solids. (see Table 2 for analytical details and isolated yields).

30 Table 2

Ex.	Structure	Starting cyclohexyl amine	Starting boronate	<i>m/z</i> (MH <sup>+</sup> )	HPLC RT (min)	Purity	% yield
-----	-----------	---------------------------	-------------------	-------------------------------	---------------	--------	---------

		structure	scale (mmol)					
614			0.24		527.3	11.66	100%	32
615			0.25		499.3	9.72	100%	79
616			0.33		539.3	11.50	100%	28
617			0.12		511.3	9.77	100%	60



618			0.10		545.2	11.36	97%	27
619			0.13		455.2	9.48	100%	61
620			0.52					

RP-HPLC analysis conditions: 5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda = 254$  nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column.

- 5 Example 621: *cis*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-4-(2-nitrophenyl)-1,3-thiazol-2-amine

The procedure described in the preparation of *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine was employed with the exception that 2-bromo-2'-nitroacetophenone (0.126 g, 0.516 mmol) was used as the alkylating agent. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS

C18, 250 x 21 mm column,  $R_f$  7.0-8.0 min) afforded *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-(2-nitrophenyl)-1,3-thiazol-2-amine as a yellow foam (0.088 g, 0.144 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_f$  7.72 min; MS (MH)<sup>+</sup> 611.

Example 622: *cis*-*N*2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzothiazol-2-amine

Pyridinium tribormide (0.894 g, 2.80 mmol) and 3,5-dimethylcyclohexanone (0.180 mL, 1.27 mmol) were suspended in dichloromethane (5 mL). The reaction mixture was stirred at ambient temperature for 24 h, then diluted with dichloromethane (60 mL). The organic layer was extracted sequentially with water (10 mL) and sodium bicarbonate (10 mL), dried (magnesium sulfate), filtered, and concentrated. Purification of the product by flash column chromatography (7.5% ethyl acetate/heptane) afforded 2,6-dibromo-3,5-dimethyl-1-cyclohexanone as a mixture of diastereomers (0.243 g, 0.855 mmol); TLC  $R_f$ (20% ethyl acetate/heptane): 0.35.

Alkylation of 2,6-dibromo-3,5-dimethyl-1-cyclohexanone (0.243 g, 0.855 mmol) was conducted using the alkylation procedure described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine, with the exception that the alkylation was conducted at 75 °C, to afford *N*-(4-bromophenyl)-*N*-(5,7-dimethyl-1,3-benzothiazol-2-yl)amine (0.251 g, 0.754 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_f$  14.8 min.

*N*-(4-Bromophenyl)-*N*-(5,7-dimethyl-1,3-benzothiazol-2-yl)amine (0.251 g, 0.754 mmol) was converted to the title compound using the procedure described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous

- ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column,  $R_t$  8.8-10.5 min) afforded *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzothiazol-2-amine as a white powder (0.081 g, 0.143 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  8.75 min; MS (MH)<sup>+</sup> 568.

- Examples 623:*cis*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,6-dihydro-4H-cyclopenta[d][1,3]thiazol-2-amine

- Cyclopentanone (200  $\mu$ L, 2.26 mmol) and pyridinium tribromide (0.723 g, 2.26 mmol) were suspended in dichloromethane (5 mL). The reaction mixture was stirred at ambient temperature overnight, then was diluted with ether/petroleum ether (1:1, 60 mL). The organic phase was extracted sequentially with water (10 mL) and aqueous sodium bicarbonate (10 mL), then was dried (magnesium sulfate), filtered, and concentrated. Purification of the product by flash column chromatography (25% ether/petroleum ether) afforded 2-bromocyclopentanone (0.220 g, 1.35 mmol) as a colorless oil; TLC (25% ether/petroleum ether)  $R_f$  0.35.
- 2-Bromocyclopentanone (0.220 g, 1.35 mmol) was converted to the title compound using the procedure described for *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-4-(2-nitrophenyl)-1,3-thiazol-2-amine, except that the alkylation reaction was conducted at 60 °C. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column,  $R_t$  7.8-8.8 min) afforded *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,6-dihydro-4H-cyclopenta[d][1,3]thiazol-2-amine as a tan powder (0.009 g, 0.017 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  7.23 min; MS (MH)<sup>+</sup> 530.

Example 624: *cis-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5-ethyl-4-phenyl-1,3-thiazol-2-amine*

The procedure for the preparation of *cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,6-dihydro-4H-cyclopenta[d][1,3]thiazol-2-amine* was used to convert butyrophenone (436  $\mu$ L, 3.00 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column,  $R_t$  8.9-11.1 min) afforded *cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5-ethyl-4-phenyl-1,3-thiazol-2-amine* as a white powder (0.022 g, 0.037 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  9.27 min; MS (MH)<sup>+</sup> 594.

15

Example 625: *cis-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine*

The procedure described for *cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,6-dihydro-4H-cyclopenta[d][1,3]thiazol-2-amine* was used to convert cyclohexanone (310  $\mu$ L, 3.00 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column,  $R_t$  6.8-8.6 min) afforded *cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine* as an orange powder (0.022 g, 0.040 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  7.62 min; MS (MH)<sup>+</sup> 544.

30

Example 626: *cis-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5-isopropyl-4-phenyl-1,3-*

## thiazol-2-amine

- The procedure described for *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine was used to convert
- 5 isovalerophenone (0.484 g, 2.98 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column, *R*<sub>t</sub> 9.5-11.7 min) afforded *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-
- 10 isopropyl-4-phenyl-1,3-thiazol-2-amine as a pink powder (0.060 g, 0.099 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column) *R*<sub>t</sub> 9.82 min; MS (MH)<sup>+</sup> 608.

- 15 Example 627: *cis*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-phenyl-5-propyl-1,3-thiazol-2-amine

- The procedure described for *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,6-
- 20 dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine was used to convert valerophenone (0.488 g, 3.01 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column, *R*<sub>t</sub> 9.6-11.8 min) afforded *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-
- 25 1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-phenyl-5-propyl-1,3-thiazol-2-amine as a yellow powder (0.135 g, 0.222 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column) *R*<sub>t</sub> 10.08 min; MS (MH)<sup>+</sup> 608.

- 30 Example 628: 3-[4-(1,3-Benzoxazol-2-ylmethyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine
- 2-Aminophenol (0.257 g, 2.36 mmol) and 4-bromophenylacetic acid (0.500

- g, 2.36 mmol) were heated neat in a sealed tube at 200 °C. After 4 h, the reaction mixture was cooled to ambient temperature and diluted with methanol/dichloromethane (5%, 60 mL). The organic phase was extracted with aqueous sodium carbonate (1 M, 10 mL), dried (magnesium sulfate), filtered, and concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate/heptane) afforded *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine as a brown solid (0.347 g, 1.20 mmol); (MH)<sup>+</sup> 290.
- N*-(1,3-Benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine was converted to 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]-1,3-benzoxazole and then to the title compound using the procedure described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-chloro-1,3-benzothiazol-2-amine. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R<sub>t</sub> 5.6-7.3 min) afforded 3-[4-(1,3-benzoxazol-2-ylmethyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a white powder (0.102 g, 0.195 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 20 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R<sub>t</sub> 6.83 min; MS (MH)<sup>+</sup> 523.

- Example 629: *N*1-[2-(Dimethylamino)ethyl]-2-{4-amino-3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}propanamide
- The procedure described in the preparation of *N*1-[2-(dimethylamino)ethyl]-2-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanamide was employed, except that the Suzuki coupling procedure employed *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R<sub>t</sub> 5.5-7.0 min) afforded *N*1-[2-(dimethylamino)ethyl]-2-{4-amino-3-[4-(1,3-benzoxazol-2-

ylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}propanamide as an off-white solid (0.003 g, 0.006 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column) *R*<sub>t</sub> 6.70 min; MS (MH)<sup>+</sup> 486.

5

Example 630: *cis*-*N*2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(4-methylphenyl)-1,3-thiazol-2-amine

*p*-Tolylboronic acid (0.150 g, 1.10 mmol), tetrakis(triphenylphosphine)pal-  
ladium(0) (0.064 g, 0.055 mmol), and cesium carbonate (1.80 g, 5.52 mmol) were  
suspended in toluene (25 mL). The reaction mixture was purged under a vigorous  
flow of nitrogen for 15 minutes. Butyryl chloride (0.344 mL, 3.31 mmol) was  
added, and the reaction mixture was heated at 100 °C under an atmosphere of  
nitrogen for 24 h. The reaction mixture was cooled to ambient temperature and  
diluted with ether (100 mL). The organic layer was extracted sequentially with  
water (10 mL), aqueous sodium bicarbonate (10 mL), and aqueous sodium chloride  
(10 mL). The organic layer was dried (magnesium sulfate), filtered, and  
concentrated. Purification of the residue by flash column chromatography (7.5 %  
ether/petroleum ether) afforded 1-(4-methylphenyl)-1-butanone as a colorless oil  
(0.134 g, 0.827 mmol): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.86 (d, 2H), 7.25 (d, 2H),  
2.92 (t, 2H), 2.41 (s, 3H), 1.76 (sx, 2H), 1.00 (t, 3H).

1-(4-Methylphenyl)-1-butanone (0.134 g, 0.827 mmol) was converted to the  
title compound using the procedure described in the preparation of *cis*-*N*2-(4-{4-  
amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-  
yl}phenyl)-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine. Purification of the  
product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium  
acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm  
column, *R*<sub>t</sub> 10.0-12.0 min) afforded *cis*-*N*2-(4-{4-amino-1-[4-(4-  
methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-  
(4-methylphenyl)-1,3-thiazol-2-amine as an off-white solid (0.036 g, 0.059 mmol);  
RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10  
min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column) *R*<sub>t</sub> 10.13

min; MS (MH)<sup>+</sup> 608.

Example 631: *cis*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(2-methylphenyl)-1,3-thiazol-2-amine

The procedure described for *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(4-methylphenyl)-1,3-thiazol-2-amine was used to convert *o*-tolylboronic acid (0.200 g, 1.47 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column, R<sub>t</sub> 9.8-11.7 min) afforded *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(2-methylphenyl)-1,3-thiazol-2-amine as an off-white solid (0.075 g, 0.123 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column) R<sub>t</sub> 9.83 min; MS (MH)<sup>+</sup> 608.

Example 632: *cis*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(3-methylphenyl)-1,3-thiazol-2-amine

The procedure described for *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(4-methylphenyl)-1,3-thiazol-2-amine was used to convert *m*-tolylboronic acid (0.175 g, 1.29 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column, R<sub>t</sub> 10.0-12.0 min) afforded *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(3-methylphenyl)-1,3-thiazol-2-amine as an off-white solid (0.051 g, 0.084 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column) R<sub>t</sub> 10.13 min; MS (MH)<sup>+</sup> 608.



Example 633: *Cis-N2*-{4-(4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl}-1*H*-2-indolecarboxamide bismaleate

- A mixture of *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.50 g, 1.15 mmol) in dichloromethane (4 mL) and pyridine (4 mL) was cooled to 0°C then treated with 1*H*-2-indolecarbonyl chloride (0.27 g, 1.49 mmol) in dichloromethane (4 mL). The mixture was allowed to warm to ambient temperature and stirred for one hour. The solvents were evaporated under reduced pressure then the residue was partitioned between dichloromethane (50 mL) and 1 N aqueous sodium hydroxide. The layers were separated then the organic solution was dried over magnesium sulfate, filtered and the filtrate concentrated under reduced pressure to yield a residue which was purified by flash chromatography on silica using dichloromethane-methanol (7:3) as mobile phase. The solid (0.53 g) was dissolved in ethyl acetate (60 mL) and ethanol (35 mL) by warming to 60°C. Maleic acid (0.32 g, 2.75 mmol) in ethyl acetate (5 mL) was added then the mixture was cooled to 0°C. The solid which formed was collected by filtration to give (0.70 g, 0.86 mmol) *Cis-N2*-{4-(4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl}-1*H*-2-indolecarboxamide bismaleate: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 11.82 (s, 1H), 9.46 (s, 1H), 8.26(s, 1H), 8.10 (d, 1H), 7.68 (d, 1H), 7.48 (d, 1H), 7.40 (s, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 7.24 (t, 1H), 7.09 (t, 1H), 6.14 (s, 4H), 4.88 (m, 1H), 3.97 (s, 3H), 2.3-3.3 (m, 14H), 2.09 (m, 2H), 1.7-1.8 (m, 4H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t<sub>r</sub> 15.22 min; MS:MH<sup>+</sup> 580.3.

Example 634: *Cis-N2*-{4-4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide bismaleate

- The title compound was prepared from *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and 1-methyl-1*H*-2-indolecarbonyl chloride in a similar manner as described for the

- preparation of *Cis-N2*-{4-(4-amino-1-(4-(4-methylpiperazino)cyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl}-1*H*-2-indolecarboxamide bismaleate: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.47 (s, 1H), 8.26(s, 1H), 8.09 (d, 1H), 7.71 (d, 1H), 7.59 (d, 1H), 7.17-7.36 (m, 4H), 7.16 (t, 1H), 6.16 (s, 4H), 4.88 (m, 1H), 3.96 (s, 3H), 2.3-3.3 (m, 14H), 2.09 (m, 2H), 1.7-1.8 (m, 4H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100Å, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t<sub>r</sub> 15.98 min; MS:MH<sup>+</sup> 594.3.
- 10 Example 635: *N1*-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide acetate
- A. 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline
- A mixture of *tert*-butyl *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (45.0 g, .129 mol) was dissolved in
- 15 dichloromethane (270 mL) then the solution was cooled to 5°C in and in ice bath. A mixture of 20% trifluoroacetic acid in dichloromethane was added dropwise over the course of one hour while maintaining the temperature of the mixture at <5°C. The reaction mixture was warmed to ambient temperature and stirred for 2 hours. The solvents were removed under reduced pressure then the resulting oil was dissolved
- 20 in dichloromethane (250 mL) and cautiously extracted with 2.5 N aqueous sodium hydroxide (300 mL) then brine (100 mL). The organic solution was dried over magnesium sulfate, filtered and the filtrate concentrated under reduced pressure to give 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (21.7 g, 67.5%) as a light brown solid bismaleate: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 7.06 (d, 1H), 6.98 (s, 1H), 8.09 (d, 1H), 6.59 (d, 1H), 5.13 (bs, 2H), 3.76 (s, 3H), 1.26 (s, 12H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100Å, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) t<sub>r</sub> 10.85 min.
- 30 B. *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate
- A mixture of *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-

- yl)-1-piperidinecarboxylate (0.50 g, 11.26 mmol), 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.10 g, 12.39 mmol), sodium carbonate (2.90 g, 27.0 mmol) and tetrakis(triphenylphosphine)palladium (0.78 g, 0.67 mmol) in ethylene glycol dimethyl ether (90 mL) and water (45 mL) was heated at 85°C for 18 hours. The mixture was cooled and evaporated under reduced pressure then partitioned between water (50 mL) and dichloromethane (150 mL). The aqueous layer was extracted further with dichloromethane (2 X 50 mL) then the combined organic solutions were dried over magnesium sulfate and then filtered. The filtrate was concentrated and purified by flash chromatography on silica gel using dichloromethane/methanol (96:4) as an eluent to provide the title compound (4.51 g, 91%) as a tan solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.04 (s, 1H), 6.98 (d, 1H), 6.76 (d, 1H), 5.06 (bs, 1H), 4.86 (m, 1H), 4.08 (m, 2H), 3.83 (s, 3H), 2.90 (m, 2H), 2.03 (m, 2H), 1.90 (m, 2H), 1.43 (s, 9H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) *t*<sub>r</sub> 9.70 min.

C. *N*1-[4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide acetate

- A mixture of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.10 g, 0.228 mmol) in dichloromethane (2 mL) and pyridine (1 mL) was treated with 2-fluoro-4-trifluoromethylbenzoyl chloride (0.057 g, 0.251 mmol) then stirred for 1 hour. The solvents were evaporated then the residue was treated with trifluoroacetic acid (1 mL) in dichloromethane (2 mL). The mixture was stirred for 1 hour at ambient temperature then the solvents were evaporated under reduced pressure and the residue purified by RP preparative HPLC on a C18 column using acetonitrile-0.05 M ammonium acetate as a mobile phase. Lyophilization afforded the pure title compound: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.90 (d, 1H), 8.31 (d, 1H), 8.24 (s, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 4.78 (m, 1H), 3.94 (s, 3H), 3.10 (m, 2H), 2.69 (m, 2H), 2.08 (m, 2H), 1.85-2.0 (m, 5H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) *t*<sub>r</sub> 17.33 min;

MS:MH<sup>+</sup> 530.2.

Examples 636-710 were prepared from *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate and appropriate acid chloride in a manner similar to that described for the preparation of *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide acetate (Example 635). In several cases functional group manipulation using standard organic chemistry techniques was required to obtain the desired compound. Free bases were obtained by partitioning the material obtained after preparative HPLC purification between aqueous sodium hydroxide and dichloromethane. The organic layer was dried over magnesium sulfate then filtered and the filtrate concentrated to provide the desired product.

Example 636: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-fluoro-4-(trifluoromethyl)benzamide acetate  
RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) *t*<sub>r</sub> 17.12 min; MS:MH<sup>+</sup> 530.2.

Example 637: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}benzamide acetate  
RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) *t*<sub>r</sub> 14.20 min; MS:MH<sup>+</sup> 444.1.

Example 638: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-phenylpropanamide acetate  
RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) *t*<sub>r</sub> 14.97 min; MS:MH<sup>+</sup> 472.2.

Example 639: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-cyclopentylpropanamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.95 min; MS:MH<sup>+</sup> 464.2.

Example 640: *N*5-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1,3-dimethyl-1*H*-5-pyrazolecarboxamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  11.62 min; MS:MH<sup>+</sup> 462.2.

Example 641: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-(2-thienyl)acetamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.17 min; MS:MH<sup>+</sup> 464.2.

Example 642: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-phenylacetamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.63 min; MS:MH<sup>+</sup> 458.2.

Example 643: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-(3,4-dimethoxyphenyl)acetamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.20 min; MS:MH<sup>+</sup> 518.3.

Example 644: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

## 2-methoxyphenyl]-2-phenoxypropanamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.43  
min; MS:MH<sup>+</sup> 488.2.

5

Example 645: N5-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-5-isoxazolecarboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  10.93  
10 min; MS:MH<sup>+</sup> 433.1.

Example 646: N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2-pyridinecarboxamide triacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
15 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.52  
min; MS:MH<sup>+</sup> 445.2.

Example 647: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2,4-difluorobenzamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  14.65  
20 min; MS:MH<sup>+</sup> 480.1.

Example 648: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2,5-difluorobenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  14.75  
25 min; MS:MH<sup>+</sup> 480.2.

Example 649: N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2-furamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

30

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.40 min; MS:MH<sup>+</sup> 434.2.

Example 650: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

5 2-methoxyphenyl}-2,2-dimethylpropanamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  14.53 min; MS:MH<sup>+</sup> 424.2.

10 Example 651: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

2-methoxyphenyl]-4-cyanobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.68 min; MS:MH<sup>+</sup> 469.2.

15

Example 652: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

2-methoxyphenyl]-1-cyclopropanecarboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  11.05 min; MS:MH<sup>+</sup> 408.2.

20

Example 653: *N*3-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

2-methoxyphenyl]-2-methylnicotinamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

25 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  11.53 min; MS:MH<sup>+</sup> 459.1.

Example 654: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

2-methoxyphenyl]-4-fluoro-3-methylbenzamide

30 RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.32 min; MS:MH<sup>+</sup> 476.2.

Example 655: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-(dimethylamino)benzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

- 5 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  14.63 min; MS:MH<sup>+</sup> 487.2.

Example 656: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2,3-difluoro-4-methylbenzamide

- 10 RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  16.03 min; MS:MH<sup>+</sup> 494.2.

Example 657: *N*4-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}isonicotinamide bisacetate

- 15 RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.77 min; MS:MH<sup>+</sup> 445.1.

- 20 Example 658: *N*3-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}nicotinamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  17.50 min; MS:MH<sup>+</sup> 445.1.

- 25 Example 659: *N*2-{[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-pyrrolicarboxamide acetate

- RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-50% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  22.20 min; MS:MH<sup>+</sup> 447.2.

Example 660: *N*3-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-



## 2-methoxyphenyl}-6-methylnicotinamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  17.97  
min; MS:MH<sup>+</sup> 459.2.

5

Example 661: N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2-pyrazinecarboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  17.63  
10 min; MS:MH<sup>+</sup> 446.1.

Example 662: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-4-iodobenzamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
15 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  16.08  
min; MS:MH<sup>+</sup> 570.1.

Example 663: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-4-bromobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
20 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.42  
min; MS:MH<sup>+</sup> 524.1.

Example 664: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-4-phenoxybenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
25 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  17.17  
min; MS:MH<sup>+</sup> 536.2.

Example 665: N1-4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-  
methoxyphenyl-4-fluorobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.65 min; MS:MH<sup>+</sup> 462.1.

Example 667: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-chlorobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.57 min; MS:MH<sup>+</sup> 478.2.

Example 668: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-methoxybenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.62 min; MS:MH<sup>+</sup> 474.2.

Example 669: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(trifluoromethoxy)benzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  16.30 min; MS:MH<sup>+</sup> 528.2.

Example 670: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-nitrobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.77 min; MS:MH<sup>+</sup> 489.2.

Example 671: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}benzo[*b*]thiophene-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  16.12 min; MS:MH<sup>+</sup> 500.2.

Example 672: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}benzo[*b*]furan-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

- 5 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.70 min; MS:MH<sup>+</sup> 484.2.

Example 673: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-methylbenzamide

- 10 RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.47 min; MS:MH<sup>+</sup> 458.2.

Example 674: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(*tert*-butyl)benzamide acetate

- 15 RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  17.93 min; MS:MH<sup>+</sup> 500.2.

- 20 Example 675: methyl 4-[(4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyanilino)carbonyl]benzoate acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  14.70 min; MS:MH<sup>+</sup> 502.1.

25

Example 676: 4-[(4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyanilino)carbonyl]benzoic acid

- RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  10.02 min; MS:MH<sup>+</sup> 478.1.
- 30

Example 677: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

2-methoxyphenyl)-2-chlorobenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min)  $t_r$  7.28  
min; MS:MH<sup>+</sup> 478.1.

5

Example 678: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2-bromobenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min)  $t_r$  7.42  
10 min; MS:MH<sup>+</sup> 524.1.

Example 679: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2-methoxybenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
15 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min)  $t_r$  7.87  
min; MS:MH<sup>+</sup> 474.2.

Example 680: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2-phenylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min)  $t_r$  8.27  
20 min; MS:MH<sup>+</sup> 520.2.

Example 681: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2-(trifluoromethyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.07  
25 min; MS:MH<sup>+</sup> 512.2.

Example 682: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-2-(trifluoromethoxy)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

30

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.77 min; MS:MH<sup>+</sup> 528.2.

Example 683: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-3-methoxybenzamide

5

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  14.43 min; MS:MH<sup>+</sup> 474.2.

Example 684: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-3-(trifluoromethyl)benzamide

10

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min)  $t_r$  8.15 min; MS:MH<sup>+</sup> 512.2.

15

Example 685: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-3-(trifluoromethyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min)  $t_r$  8.50 min; MS:MH<sup>+</sup> 530.2.

20

Example 686: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-6-(trifluoromethyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

25 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.30 min; MS:MH<sup>+</sup> 530.2.

Example 687: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-5-(trifluoromethyl)benzamide acetate

30

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  14.68 min; MS:MH<sup>+</sup> 530.2.

Example 688: N1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-5-methylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

- 5 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.32 min; MS:MH<sup>+</sup> 476.2.

Example 689: N1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-chloro-2-fluorobenzamide

- 10 RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  16.50 min; MS:MH<sup>+</sup> 496.1.

Example 690: N1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-benzoylbenzamide

- 15 RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  16.33 min; MS:MH<sup>+</sup> 548.2.

- 20 Example 691: N1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-acetylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.77 min; MS:MH<sup>+</sup> 486.2.

25

Example 692: N1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-isopropylbenzamide

- RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  17.10 min; MS:MH<sup>+</sup> 486.2.
- 30

Example 693: N1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

## 2-methoxyphenyl}-4-ethylbenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.85  
min; MS:MH<sup>+</sup> 472.2.

5

Example 694: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-4-propylbenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  17.02  
10 min; MS:MH<sup>+</sup> 486.2.

Example 695: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-4-cyclohexylbenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
15 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  19.55  
min; MS:MH<sup>+</sup> 526.2.

Example 696: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-4-ethoxybenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
20 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.28  
min; MS:MH<sup>+</sup> 488.2.

Example 697: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-4-(methylsulfonyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
25 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.01  
min; MS:MH<sup>+</sup> 527.2.

Example 698: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-  
2-methoxyphenyl}-4-isopropoxybenzamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  16.20 min; MS:MH<sup>+</sup> 502.2.

Example 699: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-4-(1H-1-imidazolyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.02 min; MS:MH<sup>+</sup> 510.2.

Example 700: N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluorobenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  14.60 min; MS:MH<sup>+</sup> 462.3.

Example 701: N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-5-methoxybenzo[b]furan-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.38 min; MS:MH<sup>+</sup> 514.3.

Example 702: N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-5-bromobenzo[b]furan-2-carboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  17.03 min; MS:MH<sup>+</sup> 564.1.

Example 703: N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-5-methylbenzo[b]furan-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  16.27 min; MS:MH<sup>+</sup> 498.3.



Example 704: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-methylbenzo[*b*]furan-2-carboxamide

- 5      RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  16.67  
min; MS:MH<sup>+</sup> 498.3.

Example 705: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-nitrobenzo[*b*]furan-2-carboxamide

- 10      RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  15.33  
min; MS:MH<sup>+</sup> 529.2.

Example 706: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-aminobenzo[*b*]furan-2-carboxamide acetate

- 15      RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  11.93  
min; MS:MH<sup>+</sup> 499.3.

- 20    Example 707: *N*2-{4-[4-(acetylamino)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-(acetylamino)benzo[*b*]furan-2-carboxamide acetate

- RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  12.47  
25    min; MS:MH<sup>+</sup> 583.2.

Example 708: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-(acetylamino)benzo[*b*]furan-2-carboxamide acetate

- 30      RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm;  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  11.95  
min; MS:MH<sup>+</sup> 541.2.

Example 709: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-7-methylbenzo[*b*]furan-2-carboxamide acetate

- RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm);  
5 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  14.23 min; MS:MH<sup>+</sup> 498.3.

Example 710: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-7-methoxybenzo[*b*]furan-2-carboxamide acetate

- 10 RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5  $\mu$ m, 100A, 250 X 4.6 mm);  
5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min)  $t_r$  13.03 min; MS:MH<sup>+</sup> 514.3.

Example 711: *rac-N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

- 15  
A. *rac-tert*-butyl 3-hydroxy-1-pyrrolidinecarboxylate  
To a solution of 3-pyrrolidinol (3.144 g, 3.00 mL, 36.09 mmol) in 1,4-dioxane (50 mL) and water (50 mL) was added di-*tert*-butyl dicarbonate (8.664 g, 39.70 mmol) and sodium bicarbonate (10.612 g, 126.3 mmol). The mixture was stirred at room temperature for 18 h to afford a white suspension in a yellow solution. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine, dried  
25 over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac-tert*-butyl 3-hydroxy-1-pyrrolidinecarboxylate as a pale yellow oil (6.039 g, 89%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  1.51 (s, 9 H), 1.84-2.05 (m, 2 H), 2.28 (d, 1 H), 3.33-3.48 (m, 4 H), 4.43 (s, 1H).

- 30 B. *rac*-3-Iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride

To a solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.610 g,

21.49 mmol) in tetrahydrofuran (200 mL) was added *rac-tert*-butyl 3-hydroxy-1-pyrrolidinecarboxylate (6.039 g, 32.25 mmol), triphenylphosphine (11.273 g, 42.98 mmol), and diethyl azodicarboxylate (7.485 g, 6.77 mL, 42.98 mmol). The reaction mixture was stirred at room temperature for 6 days and then concentrated to afford an orange-brown oil. Acetone (100 mL) and 5 N hydrochloric acid (50 mL) were added and the solution was heated at 40 °C for 18 h and then cooled to room temperature. The resulting yellow precipitate was filtered, and the filter cake was washed with diethyl ether and dried to afford *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride as an off-white solid (5.153 g, 65%). RP-HPLC Rt 4.079 min, 99% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); *m/z* 331 (*MH*<sup>+</sup>).

C. *rac*-3-Iodo-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride (0.400 g, 1.09 mmol) in dichloroethane (10 mL) was added formaldehyde (37% in water, 0.12 mL, 1.63 mmol), sodium triacetoxymethylborohydride (0.578 g, 2.73 mmol), and acetic acid (0.37 mL, 6.55 mmol). The reaction mixture was stirred at room temperature for 3 days and then additional formaldehyde (37% in water, 0.12 mL, 1.63 mmol), sodium triacetoxymethylborohydride (0.578 g, 2.73 mmol), and acetic acid (0.37 mL, 6.55 mmol) were added. The reaction mixture stirred for an additional 3 h and was then concentrated to afford *rac*-3-iodo-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a pale yellow solid (0.639 g) which was used in subsequent reactions without further purification. RP-HPLC Rt 4.226 min, 96% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); *m/z* 345 (*MH*<sup>+</sup>).

D. *N*2-(4-Bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

1,1'-Thiocarbonyldi-2(1*H*)-pyridone (1.418 g, 6.104 mmol) was added to a solution of 4-bromoaniline (1.000 g, 5.813 mmol) in dichloromethane (50 mL). The

purple solution was stirred at room temperature for 30 min and then washed with water (50 mL) and 0.5 N hydrochloric acid (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford a purple solid. 6-Amino-2,4-xylenol (0.837 g, 6.104 mmol) and toluene (50 mL) were added and the mixture was  
5 heated at 80 °C for 30 min. 1,3-Dicyclohexylcarbodiimide (1.799 g, 8.720 mmol) was added, and the solution was heated at 80 °C for 48 h and then cooled to room temperature. The resulting precipitate was filtered, and the filter cake was washed with dichloromethane (50 mL) to afford *N*2-(4-bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine as a pale orange solid (1.215 g, 66%). RP-HPLC Rt 17.643  
10 min, 86% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); *m/z* 317 (*MH*<sup>+</sup>).

E. *N*2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine  
15

*N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from *N*2-(4-bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (1.215 g, 3.831 mmol) in a manner similar to that used for the preparation of *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-  
20 1,3-benzoxazol-2-amine. The compound was formed as a tan powder (0.880 g, 63%). RP-HPLC (25 to 100 % CH<sub>3</sub>CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) Rt=14.48 min, 81%; *m/z* 365 (*MH*<sup>+</sup>).

F. *rac-N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine  
25

*rac-N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine was  
30 prepared from *rac*-3-iodo-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.581 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.265 g, 0.726

mmol) in a manner similar to that used for the preparation of *cis*-N2-(4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a white powder (0.062 g, 23%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 2.39 (s, 3 H), 2.32-2.40 (m, 3 H), 2.40 (s, 3 H), 2.75-2.80 (m, 2 H), 3.08 (t, 1 H), 3.26 (s, 3 H), 5.40 (m, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.85 (s, 1 H); RP-HPLC Rt 10.905 min, 96% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 455 (*MH*<sup>+</sup>).

10

Example 712: *rac*-N2-(4-[4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A. *rac*-3-Iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

15

To a solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine mono hydrochloride (0.350 g, 1.09 mmol) in *N,N*-dimethylformamide (10 mL) was added 2-bromoethylmethyl ether (0.159 g, 0.11 mL, 1.15 mmol), potassium carbonate (0.462 g, 3.34 mmol), and potassium iodide (0.008 g, 0.05 mmol). The reaction mixture stirred at 65 °C for 18 h and then additional 2-bromoethylmethyl ether (0.066 g, 0.040 mL, 0.48 mmol), potassium carbonate (0.130 g, 0.940 mmol), and potassium iodide (0.008 g, 0.05 mmol) were added. The reaction mixture was stirred for an additional 18 h and was then concentrated. The residue was partitioned between dichloromethane (10 mL) and water (10 mL). The organic phase was separated, washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a yellow solid (0.313 g, 84%) which was used in subsequent reactions without further purification. RP-HPLC Rt 5.089 min, 80% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 389 (*MH*<sup>+</sup>).

30

B. *rac*-N2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

*rac*-N2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.250 g, 0.515 mmol) and N2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.235 g, 0.644 mmol) in a manner similar to that used for the preparation of *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a yellow powder (0.185 g, 72%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 2.30-2.49 (m, 2 H), 2.41 (s, 3 H), 2.49 (s, 3 H), 2.66 (m, 2 H), 2.78 (m, 2 H), 3.17 (m, 2 H), 3.24 (s, 3 H), 3.45 (t, 2 H), 5.40 (m, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.85 (s, 1 H); RP-HPLC Rt 11.477 min, 96% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 499 (*MH*<sup>+</sup>).

20 Example 713: *Cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A. N2-(4-Bromo-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine  
N2-(4-Bromo-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was

25 prepared from 4-bromo-2-fluoroaniline (2.000 g, 10.53 mmol) in a manner similar to that used for the preparation of N2-(4-bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine. The compound was formed as a pink solid (1.916 g, 54%). RP-HPLC Rt 17.96 min, 95% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 337 (*MH*<sup>+</sup>).

B. N2-[2-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine

*N*2-[2-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from *N*2-(4-bromo-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (6.500 g, 19.39 mmol) in a manner similar to that used for the preparation of *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine. The compound was formed as a pink solid (3.549 g, 48 %). RP-HPLC (25 to 100 % CH<sub>3</sub>CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) Rt=15.50 min, 78%; *m/z* 383 (*MH*<sup>+</sup>).

- 10 C. *Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

*Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.453 mmol) and *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.216 g, 0.566 mmol) in a manner similar to that used for the preparation of *cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a pale yellow powder (0.111 g, 43%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 1.56-1.83 (m, 4 H), 2.15 (s, 3 H), 2.22-2.55 (m, 12 H), 2.34 (s, 3 H), 2.41 (s, 3 H), 3.22-3.53 (m, 1 H), 4.78-4.83 (m, 1 H), 6.81 (s, 1 H), 7.10 (s, 1 H), 7.45-7.53 (m, 2 H), 8.23 (s, 1 H), 8.49 (t, 1 H), 10.59 (s, 1 H); RP-HPLC Rt 11.873 min, 95% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 570 (*MH*<sup>+</sup>).

Example 714: *Cis*-3-(4-imidazo[1,2-*a*]pyridin-2-ylphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

- A. 2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]imidazo[1,2-*a*]pyridine  
2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]imidazo[1,2-

- a*]pyridine was prepared from 2-(4-bromophenyl)imidazo[1,2-*a*]pyridine (0.273 g, 1.00 mmol) in a manner similar to that used for the preparation of *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine. The compound was formed as a white solid (0.250 g, 78 %). RP-HPLC (25 to 100 % CH<sub>3</sub>CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) Rt=11.35 min, 87%; *m/z* 321 (*MH*<sup>+</sup>).
- 5

B. *Cis*-3-(4-imidazo[1,2-*a*]pyridin-2-ylphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

10

- Cis*-3-(4-imidazo[1,2-*a*]pyridin-2-ylphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine was prepared from *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.453 mmol) and 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]imidazo[1,2-*a*]pyridine (0.250 g, 0.679 mmol) in a manner similar to that used for the preparation of *cis*-*N*2-[4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-fluorophenyl]-1,3-benzoxazol-2-amine. The compound was formed as a white powder (0.021 g, 9%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 1.57-1.73 (m, 4 H), 2.08-2.50 (m, 12 H), 2.16 (s, 3 H), 3.37 (m, 1 H), 4.82 (m, 1 H), 6.92 (t, 1 H), 7.27 (t, 1 H), 7.61 (d, 1 H), 7.74 (d, 2 H), 8.15 (d, 2 H), 8.24 (s, 1 H), 8.56 (d, 1 H); RP-HPLC Rt 8.16 min, 97% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 508 (*MH*<sup>+</sup>).
- 15
- 20

25

Example 715: *rac*-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone

- A. *rac*-1-[3-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone
- 30

To a solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride (0.367 g, 1.00 mmol) in dichloromethane (10 mL) was added 2-(dimethylamino)acetic acid (0.134 g, 1.30 mmol), 1-hydroxy-



- 7-azabenzotriazole (0.150 g, 1.10 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.249 g, 1.30 mmol), and diisopropylethyl amine (0.65 g, 0.87 mL, 5.0 mmol). The reaction mixture stirred at room temperature for 18 h and was then poured into water (10 mL). The organic phase was separated and washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac*-1-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone as a yellow-orange solid (0.278 g, 67%) which was used in subsequent reactions without further purification. RP-HPLC Rt 4.881 min, 80% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); *m/z* 416 (*MH*<sup>+</sup>).

- B. *rac*-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone
- rac*-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone was prepared from *rac*-1-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone (0.278 g, 0.669 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.305 g, 0.837 mmol) in a manner similar to that used for the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a white powder (0.219g, 62%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 2.17 (s, 3 H), 2.23 (s, 3 H), 2.3-2.50 (m, 4 H), 2.34 (s, 3 H), 2.40 (s, 3 H), 2.99-4.26 (m, 4 H), 5.44-5.49 (m, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.65 (d, 2 H), 7.92 (d, 2 H), 8.26 (s, 1 H), 10.86 (s, 1 H); RP-HPLC Rt 10.765 min, 96% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); *m/z* 526 (*MH*<sup>+</sup>).

Example 716: *rac*-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-

1-pyrrolyl]-2-methyl-2-(methylamino)-1-propanone

- A. *rac*-9*H*-9-Fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate

5 To a solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride (0.100 g, 0.273 mmol) in dichloromethane (5 mL) was added 2-[[9*H*-9-fluorenylmethoxy]carbonyl](methyl)amino]-2-methylpropanoic acid (0.120 g, 0.354 mmol), 1-hydroxy-7-azabenzotriazole (0.041 g, 0.30 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
10 (0.068 g, 0.35 mmol), and diisopropylethyl amine (0.18 g, 0.24 mL, 1.4 mmol). The reaction mixture was stirred at room temperature for 5 h and then poured into water (10 mL). The organic phase was separated and washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac*-9*H*-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-  
15 yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate as a yellow solid (0.223 g) which was used in subsequent reactions without further purification. RP-HPLC Rt 13.688 min, 63% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1 mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); *m/z* 652 (*MH*<sup>+</sup>).

20

- B. *rac*-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-methyl-2-(methylamino)-1-propanone

To a solution of *rac*-9*H*-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl}-  
25 *N*-methylcarbamate (0.178 g, 0.273 mmol) in ethylene glycol dimethyl ether (6 mL) and water (3 mL) was added *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.124 g, 0.341 mmol), tetrakis(triphenylphosphine) palladium (0) (0.016 g, 0.014 mmol), and sodium  
30 carbonate (0.072 g, 0.683 mmol). The solution was heated at 80 °C for 18 h, and then cooled to room temperature. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was separated and washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and

concentrated to afford *rac*-9*H*-9-fluorenylmethyl *N*-2-[3-(4-amino-3-4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl-*N*-methylcarbamate as a pale brown oil (0.223 g), which was used in the next step without further purification.

- 5 A solution of *rac*-9*H*-9-fluorenylmethyl *N*-2-[3-(4-amino-3-4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl-*N*-methylcarbamate (0.223 g) in  $N,N$ -dimethylformamide (4 mL) was treated with piperidine (0.8 mL), and the reaction mixture stirred at room temperature for 18 h. The green solution was partitioned
- 10 between dichloromethane (10 mL) and water (10 mL). The organic phase was separated and washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford a dark green oil. Purification by preparative RP-HPLC (25 to 100 %  $\text{CH}_3\text{CN}$  in 0.1 *N* aqueous ammonium acetate over 20 min at 21 mL/min using a 8  $\mu\text{m}$  Hypersil HS C18, 250 x 21 mm column,  $R_t$  = 6.7-8.1 min)
- 15 afforded *rac*-1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl})-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-methyl-2-(methylamino)-1-propanone as an off-white solid (0.085 g, 58%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz) Major rotamer: 1.20 (s, 6 H), 1.96 (s, 3 H), 2.3-2.50 (m, 3 H), 2.34 (s, 3 H), 2.40 (s, 3 H), 3.17-4.44 (m, 4 H), 5.42 (s, 1 H), 6.80 (s, 1 H),
- 20 7.11 (s, 1 H), 7.63 (d, 2 H), 7.91 (d, 2 H), 8.26 (s, 1 H), 10.85 (s, 1 H); Minor rotamer: 1.15 (s, 6 H), 2.15 (s, 3 H), 2.3-2.50 (m, 3 H), 2.34 (s, 3 H), 2.40 (s, 3 H), 3.17-4.44 (m, 4 H), 5.42 (s, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.63 (d, 2 H), 7.91 (d, 2 H), 8.26 (s, 1 H), 10.85 (s, 1 H); RP-HPLC  $R_t$  10.994 min, 95% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at
- 25 1 mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu\text{m}$ , 150 x 3.9 mm column);  $m/z$  540 ( $MH^+$ ).

Example 717: *rac*-*N*2-[4-(4-Amino-1-tetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine

- 30 A. *rac*-*tert*-Butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate

A solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride (0.500 g, 1.36 mmol), sodium bicarbonate

(0.401 g, 4.77 mmol), and di-*tert*-butyl dicarbonate (0.327 g, 1.50 mmol) in 1,4-dioxane (8 mL) and water (8 mL) was stirred at room temperature for 3 h. The resulting off-white suspension was filtered, and the filter cake was washed with water (10 mL) and dried to afford *rac-tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-  
5 *d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate as an off-white solid (0.412 g, 70%). RP-HPLC Rt 11.540 min, 100% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1 mL/min;  $\lambda = 254$  nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $m/z$  431 ( $MH^+$ ).

10           B.     *rac-N2*-[4-(4-Amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-  
                  *d*]pyrimidin-3-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine  
To a solution of *rac-tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate (0.412 g, 0.958 mmol) in ethylene glycol dimethyl ether (6 mL) and water (3 mL) was added *N2*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-  
15 2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.436 g, 1.20 mmol), tetrakis(triphenylphosphine) palladium (0) (0.055 g, 0.048 mmol), and sodium carbonate (0.254 g, 2.39 mmol). The solution was heated at 80 °C for 18 h, and then cooled to room temperature. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was separated and  
20 washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac-tert*-butyl 3-(4-amino-3-[4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate as an orange solid (1.029 g), which was used in the next step without further purification.  
25           6 N Hydrochloric acid (10 mL) was added to a solution of *rac-tert*-butyl 3-(4-amino-3-[4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl]-1*H*-pyrazolo[3,4-  
                  *d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate (1.029 g) in acetone (10 mL) and the reaction mixture was stirred at 45 °C for 5 h. The reaction mixture was filtered, and the resulting opaque filtrate was concentrated to afford an orange solid. Purification  
30 by preparative RP-HPLC (25 to 100 %  $CH_3CN$  in 0.1 N aqueous ammonium acetate over 20 min at 21 mL/min using a 8  $\mu$ m Hypersil HS C18, 250 x 21 mm column,  $t_r = 6.2$ -7.5 min) afforded *rac-N2*-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-

pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine as an off-white solid (0.148 g, 35%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 2.15-2.22 (m, 2 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 2.93-4.04 (m, 5 H), 5.31 (m, 1 H), 6.79 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.85 (s, 1 H); RP-HPLC Rt

- 5 10.603min, 99% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 441 (*MH*<sup>+</sup>).

Example 718: *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-

- 10 pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl]-7-isopropyl-1,3-benzoxazol-2-amine diacetate

A. 2-Amino-6-isopropylphenol

- A solution of 6-isopropyl-2-nitrophenol (3.000 g, 16.56 mmol) and sodium hydrosulfite (11.53 g, 66.23 mmol) in ethanol (180 mL) and water (90 mL) was stirred at 80 °C for 20 h and then cooled to room temperature. The resulting orange solution was concentrated and then partitioned between dichloromethane (50 mL) and water (50 mL). The organic phase was separated and washed with brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 2-amino-6-isopropylphenol as an orange solid (1.792 g, 72 %). RP-HPLC Rt 8.171 min, 92% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 150 (*M-H*<sup>-</sup>).

B. *N2*-(4-Bromophenyl)-7-isopropyl-1,3-benzoxazol-2-amine

- A solution of 2-amino-6-isopropylphenol (0.354 g, 2.34 mmol) and 4-bromophenylisothiocyanate (0.500 g, 2.34 mmol) in tetrahydrofuran (35 mL) was stirred at room temperature for 3 h. Anhydrous copper (II) sulfate (3.361 g, 21.06 mmol), silica gel (3.361 g), and triethylamine (0.236 g, 0.33 mL, 2.34 mmol) were added, and the mixture stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite and the washed with diethyl ether (3 x 50mL). The filtrate was concentrated to afford a brown solid. The solid material was applied to silica gel and passed through a pad a silica gel along with ethyl acetate (3 x 50mL). The filtrate was concentrated to afford *N2*-(4-bromophenyl)-7-isopropyl-

1,3-benzoxazol-2-amine (0.702 g, 91 %). RP-HPLC Rt 18.066 min, 86% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $m/z$  333 ( $MH^+$ ).

5

C. *N*2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-7-isopropyl-1,3-benzoxazol-2-amine

*N*2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-7-isopropyl-1,3-benzoxazol-2-amine was prepared from *N*2-(4-bromophenyl)-7-isopropyl-1,3-benzoxazol-2-amine (0.412 g, 1.24 mmol) in a manner similar to that used for the preparation of *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.346 g, 74 %). RP-HPLC Rt 18.964 min, 79% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $m/z$  379 ( $MH^+$ ).

15

D. *Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-isopropyl-1,3-benzoxazol-2-amine diacetate

*Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-isopropyl-1,3-benzoxazol-2-amine diacetate was prepared from *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.250 g, 0.566 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-7-isopropyl-1,3-benzoxazol-2-amine (0.339 g, 0.708 mmol) in a manner similar to that used for the preparation of *cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.205 g, 64%).  $^1H$  NMR (DMSO- $d_6$ , 400 MHz) 1.36 (d, 6 H), 1.56-2.50 (m, 16 H), 1.90 (6 H), 2.15 (s, 3 H), 3.23-3.28 (m, 2 H), 4.80 (m, 1 H), 7.04 (d, 1 H), 7.18 (t, 1 H), 7.34 (d, 1 H), 7.66 (d, 2 H), 7.96 (d, 2 H), 8.24 (s, 1 H); RP-HPLC Rt 12.508 min, 100% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $m/z$  566 ( $MH^+$ ).

30

Example 719: *N2*-(4-{4-Amino-1-[(3*S*)-1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine monoacetate

5

*N2*-(4-{4-Amino-1-[(3*S*)-1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine monoacetate was prepared from (*R*)-(+)-3-pyrrolidinol in a manner analogous to that used for the preparation of *rac-N2*-(4-{4-amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine. The compound was formed as a pink solid (0.103 g, 53%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 1.89 (s, 3 H), 2.28-2.31 (m, 2 H), 2.35 (s, 3 H), 2.40 (s, 3 H), 2.65 (t, 2 H), 2.73-2.87 (m, 2 H), 3.17 (t, 2 H), 3.24 (s, 3 H), 3.45 (t, 2 H), 5.37 (m, 1 H), 6.79 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.59 (s, 2 H); RP-HPLC Rt 11.607 min, 95% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 499 (*MH*<sup>+</sup>).

Example 720: *rac-N2*-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine monoacetate

20

*rac-N2*-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine monoacetate was prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.319 mmol) and *N2*-(4-{4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine (0.145 g, 0.399 mmol) in a manner similar to that used for the preparation of *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a white solid (0.082 g, 52%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 1.23 (t, 3 H), 1.90 (s, 3 H), 2.33-3.47 (m, 10 H), 2.66 (q, 2 H), 3.25 (s, 3 H), 5.40 (m, 1 H), 6.99 (d, 1 H), 7.33 (s, 1 H), 7.40 (d, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.25 (s, 1 H), 10.81 (s, 1 H); RP-HPLC Rt 11.781 min, 93% purity (5% to 85% acetonitrile/0.1M

25

30

aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $m/z$  499 ( $MH^+$ ).

Example 721: *rac*-N2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1H-3-

- 5                   pyrrolyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-methyl-1,3-benzoxazol-2-amine monoacetate

*rac*-N2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine monoacetate was prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1H-3-

- 10 pyrrolyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.319 mmol) and N2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-methyl-1,3-benzoxazol-2-amine (0.145 g, 0.399 mmol) in a manner similar to that used for the preparation of *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was
- 15 formed as an off-white solid (0.038 g, 16%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 1.91 (s, 3 H), 2.33 (m, 2 H), 2.39 (s, 3 H), 2.66 (m, 2 H), 2.75-2.83 (m, 3 H), 3.17 (t, 1 H), 3.29 (s, 3 H), 3.45 (t, 2 H), 5.37 (m, 1 H), 6.96 (d, 1 H), 7.30 (s, 1 H), 7.38 (d, 1 H), 7.67 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.80 (s, 1 H); RP-HPLC Rt 10.756 min, 100% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to
- 20 pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $m/z$  485 ( $MH^+$ ).

Example 722: N2-(4-{4-Amino-1-[(3*R*)-1-(2-methoxyethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-

- 25                   1,3-benzoxazol-2-amine diacetate

N2-(4-{4-Amino-1-[(3*R*)-1-(2-methoxyethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine diacetate was prepared from (*S*)-(-)-3-pyrrolidinol in a manner analogous to that used for the preparation of *rac*-N2-(4-{4-amino-1-[1-(2-methoxyethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.214 g, 39%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 1.89 (s, 6 H), 2.28-2.31 (m, 2 H), 2.35 (s, 3 H), 2.40 (s, 3 H), 2.65 (t, 2 H), 2.73-2.87 (m, 2 H), 3.17 (t, 2 H), 3.24 (s, 3 H), 3.45 (t, 2 H), 5.37 (m, 1

30



H), 6.79 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H); RP-HPLC Rt 11.674 min, 97% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $m/z$  499 ( $MH^+$ ).

5

Example 723: *Rac-N2*-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1H-3-pyrryl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-chloro-1,3-benzoxazol-2-amine monoacetate

- rac-N2*-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1H-3-pyrryl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-chloro-1,3-benzoxazol-2-amine monoacetate was prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1H-3-pyrryl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.319 mmol) and *N2*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-chloro-1,3-benzoxazol-2-amine (0.148 g, 0.399 mmol) in a manner similar to that used for the preparation of
- cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.080 g, 50%).  $^1H$  NMR (DMSO- $d_6$ , 400 MHz) 1.91 (s, 3 H), 2.33 (m, 2 H), 2.66 (m, 2 H), 2.75-2.85 (m, 3 H), 3.17 (t, 1 H), 3.24 (s, 3 H), 3.45 (t, 2 H), 5.37 (m, 1 H), 7.18 (d, 1 H), 7.55 (d, 2 H), 7.68 (d, 2 H), 7.92 (d, 2 H), 8.24 (s, 1 H), 9.80 (s, 1 H); RP-HPLC Rt 11.337 min, 97% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $m/z$  505 ( $MH^+$ ).

- Example 724: *trans-N1*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-phenylpropanamide

- A solution of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.700 g, 1.6 mmol) in pyridine (11 mL) at 0°C was treated with hydrocinnamoyl chloride (0.324 g, 1.92 mmol). The reaction mixture was stirred at 0°C for 20 min and the ice bath was removed to stir at room temperature. The reaction was complete after 5.5 hours. Sodium hydroxide solution (1 N, 20 mL) was added and stirred for 30 minutes. The

- organic layer was removed under reduced pressure. Dichloromethane (20 mL) was added, and the layers were partitioned. The aqueous layer was extracted with dichloromethane (80 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a gradient of 5% methanol in dichloromethane to 50% methanol in dichloromethane on a 35 g ISCO silica gel column to give 0.569 g (63%) of *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-phenylpropanamide. *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-phenylpropanamide (0.569 g, 1 mmol) in warmed ethyl acetate was treated with a warmed solution of maleic acid (0.384 g, 3 mmol) in ethyl acetate. The formed precipitate was filtered under a nitrogen atmosphere and dried under high vacuum to give the tri maleate salt. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 9.238 (s, 1H), 8.2216 (s, 1H), 8.1991-8.1786 (d, 1H, *J* = 8.2 Hz), 7.3147-7.2664 (m, 4H), 7.2366-7.2330 (m, 1H), 7.2026-7.1732 (dd, 2H), 6.171 (s, 6H), 4.6649-4.6083 (m, 1H), 4.0948-4.0697 (m, 1H), 3.8916 (s, 3H), 3.1750-3.1632 (d, 2H, *J* = 4.72 Hz), 2.9364-2.8984 (m, 2H), 2.7885-2.7506 (m, 2H), 2.5290 (s, 2H), 2.3905-2.3231 (m, 4H), 2.1489 (s, 3H), 2.0549-1.9243 (m, 6H), 1.4821-1.4457 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3 μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium Acetate in Water to 95% Acetonitrile over 6 min, 0.8 to 0.5 mL/min) R<sub>t</sub> 1.75 min (100%), M<sup>+</sup> 569.4.

- Example 725: *trans*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

- A suspension of *trans*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide di-maleate (0.200 g, 0.242 mmol) in dichloromethane (15 mL) was treated with 1N sodium hydroxide solution. The reaction mixture was stirred for 1 h at room temperature. The layers were partitioned using an Empore extraction cartridge. The organic layer was removed by

blowing nitrogen over the top of the solvent to give 0.072 g (50%) of *trans*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 9.4355 (s, 1H), 8.2464 (s, 1H), 8.1241-8.1037 (d, 1H, *J* = 8.16 Hz), 7.7186-7.6987 (d, 1H, *J* = 7.96 Hz), 7.6005-7.5795 (d, 1H, *J* = 8.4 Hz), 7.3532-7.2795 (m, 4H), 7.1717-7.1343 (t, 1H), 4.6833 (m, 1H), 4.0560 (s, 3H), 3.9573 (s, 3H), 2.6704 (m, 6H), 2.4404 (m, 2H), 2.2953 (s, 6H), 2.1282-1.9889 (m, 5H), 1.5124 (m, 2H). The compound was directly used in the subsequent reaction without purification.

10 Example 726: *trans*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide di-mesylate

A warmed solution of *trans*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.072 g, 0.12 mmol) in ethyl acetate (20 mL) was treated with methane sulfonic acid (0.012 g, 0.12 mmol). A precipitate slowly formed and was filtered under a nitrogen atmosphere to give 0.051 g of *trans*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide di-mesylate. The melting range was determined to be 345.5 to 348.1°C. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 9.4353 (s, 1H), 8.2461 (s, 1H), 8.1239-8.1035 (d, 1H, *J* = 8.16 Hz), 7.7182-7.6985 (d, 1H, *J* = 7.88 Hz), 7.6004-7.5792 (d, 1H, *J* = 8.48 Hz), 7.3442-7.2794 (m, 4H), 7.1718-7.1349 (t, 1H), 4.6829 (m, 1H), 4.0396 (s, 3H), 3.9570 (s, 3H), 2.6703 (m, 6H), 2.5 (s, 3H), 2.2949 (s, 6H), 2.0891-2.9086 (m, 7 H), 1.5179 (m, 2H).

Example 727: 3-(4-Amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

30 A. 3-Iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine  
3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (500 mg, 1.45 mmol), formaldehyde (30% solution in water, 0.16 mL, 1.60 mmol) and sodium

- triacetoxyborohydride (430 mg, 2.03 mmol) were mixed in 1,2-dichloroethane (5 mL). The reaction mixture was stirred at room temperature for 4 hours. Saturated sodium bicarbonate solution was added to adjust the pH to about 8. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over  $\text{MgSO}_4$ , filtered and evaporated to give 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (275 mg, 53%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.85 (m, 2H), 2.09 (m, 4H), 2.22 (s, 3H), 2.88 (m, 2H), 4.75 (m, 1H), 8.19 (s, 1H), 8.32 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3  $\mu\text{m}$ , 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.):  $\text{MH}^+$  359.0,  $R_t=0.46\text{min}$ .

- B. *tert*-Butyl *N*-(4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)carbamate
- 3-Iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (270 mg, 0.754 mmol), *tert*-butyl *N*-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (290 mg, 0.829 mmol), palladium tetrakis(triphenylphosphine) (52 mg, 0.045 mmol) and sodium carbonate (192 mg, 1.81 mmol) were mixed in ethylene glycol dimethyl ether (8 mL) and water (4 mL). The reaction mixture was heated at reflux overnight under nitrogen. Organic solvent was removed under reduced pressure and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water then brine, dried over  $\text{MgSO}_4$ , filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (90:10 to 70:30) as mobile phase to give *tert*-butyl *N*-(4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)carbamate (250 mg, 73%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.48 (s, 9H), 1.88 (m, 2H), 2.10 (m, 2H), 2.24 (m, 5H), 2.92 (m, 2H), 3.69 (s, 3H), 4.64 (m, 1H), 7.21 (m, 2H), 7.91 (d,  $J=8.16$  Hz, 1H), 8.04 (s, 1H), 8.23 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3  $\mu\text{m}$ , 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.):  $\text{MH}^+=454.2$ ,  $R_t=1.67$  min.

C. 3-(4-Amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine

A mixture of trifluoroacetic acid/dichloromethane (20:80, 7 mL) was added to a solution of *tert*-butyl *N*-{4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl} carbamate (240 mg, 0.529 mmol) in dichloromethane (4 mL) at 0°C. 15 minutes later, the ice-bath was removed and the reaction mixture was stirred at room temperature for 4 hours. The solvents were evaporated and the residue was dissolved in dichloromethane. Sodium hydroxide (1.0N) was added to adjust the pH to about 10. The layers were separated and the aqueous layer was extracted with dichloromethane four times. The combined organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated to give 3-(4-amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (178 mg, 95%). HPLC (Waters 486 - Column: delta pak, C18, 5 um, 300 Å, 150x3.9 mm. Eluents: 5% B/A to 95% B/A in 10 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 1.0 mL/min.) R<sub>t</sub>=6.45 min.

Example 728: *N*1-{4-[4-Amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenyl-1-cyclopropanecarboxamide

*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride (31 mg, 0.170 mmol) in dichloromethane (0.3 mL) was added to a solution of 3-(4-amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (60 mg, 0.17 mmol) in pyridine (1.2 mL) at 0°C. After 5 minutes, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 1 hours then, more *trans*-2-Phenyl-1-cyclopropanecarbonyl chloride (15 mg, 0.083 mmol) was added. After 2 hours, the solvent was evaporated and the residue was purified by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) as mobile phase to give *N*1-{4-[4-Amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenyl-1-cyclopropanecarboxamide (75 mg, 89%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.42 (m, 1H), 1.77 (m, 1H), 1.85 (m, 1H), 2.03 (m, 1H), 2.24 (m, 2H), 2.37 (s, 3H), 2.46 (m, 2H), 2.62 (m, 1H), 3.05 (m, 2H), 3.96 (s, 3H), 4.77 (m, 1H), 5.69 (s, 2H), 7.24 (m, 7H), 8.11 (s, 1H), 8.35 (m, 1H), 8.45 (d, J=8.38 Hz, 1H).

LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.):  $MH^+$ =498.3,  $R_t$ =1.84 min.

5

Example 729: *N*1-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(trifluoromethyl)benzamide  
4-(Trifluoromethyl)-1-benzenecarbonyl chloride (35 mg, 0.170 mmol) in dichloromethane (0.3 mL) was added to a solution of 3-(4-amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (60 mg, 0.17 mmol) in pyridine (1.2 mL) at 0°C. After 5 minutes, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 1 hours then, more 4-(trifluoromethyl)-1-benzenecarbonyl chloride (18 mg, 0.086 mmol) was added. 2 hours later, the solvent was evaporated and the residue was purified by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) as mobile phase to give *N*1-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(trifluoromethyl)benzamide (85 mg, 95%).  $^1H$  NMR ( $CDCl_3$ )  $\delta$  2.10 (m, 2H), 2.37-2.59 (m, 7H), 3.15 (m, 2H), 4.02 (s, 3H), 4.83 (m, 1H), 5.68 (s, 2H), 7.34 (m, 2H), 7.80 (d,  $J$ =8.21 Hz, 2H), 8.04 (d,  $J$ =8.10 Hz, 2H), 8.38 (s, 1H), 8.67 (m, 2H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.):  $MH^+$ =526.3,  $R_t$ =1.93 min.

25 Example 730: *N*1-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(trifluoromethoxy)benzamide  
4-(Trifluoromethoxy)-1-benzenecarbonyl chloride (38 mg, 0.170 mmol) in dichloromethane (0.3 mL) was added to a solution of 3-(4-amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (60 mg, 0.17 mmol) in pyridine (1.2 mL) at 0°C. After 5 minutes, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 1 hours then, more 4-(trifluoromethyl)-1-benzenecarbonyl chloride (19 mg, 0.085 mmol) was added. After 2 hours, the solvent was evaporated and the residue was purified by flash

column chromatography using dichloromethane/methanol (95:5 to 70:30) as mobile phase to give N1-[4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-4-(trifluoromethoxy)benzamide (70 mg, 76%).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.06 (d, J=11.79 Hz, 2H), 2.28 (m, 2H), 2.40 (s, 3H), 2.50 (m, 2H), 3.07 (d, J=10.8 Hz, 2H), 4.02 (s, 3H), 4.80 (m, 1H), 5.71 (s, 2H), 7.27 (m, 2H), 7.36 (d, J=8.20 Hz, 2H), 7.98 (d, J=6.20Hz, 2H), 8.37 (s, 1H), 8.59 (s, 1), 8.67 (d, J=8.55 Hz, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=542.3, R<sub>t</sub>=1.98 min.

Example 731: *cis*-1-[4-(4-Methylpiperazino)cyclohexyl]-3-[4-(1,3-oxazol-5-yl)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine  
A. 4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]benzaldehyde  
*cis*-3-Methyl-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine (3.0 g, 6.80 mmol), 4-formylphenylboronic acid (1.22 g, 8.16 mmol), palladium tetrakis(triphenyl)phosphine (0.47 g, 0.41 mmol) and sodium carbonate (1.73 g, 16.31 mmol) were mixed with ethylene glycol dimethyl ether (70 mL) and water (35 mL). The reaction mixture was heated at reflux overnight under nitrogen. Organic solvent was removed under reduced pressure and the aqueous layer was filtered and washed with water. After drying on the lyophilizer, the residue was purified by flash column chromatography using dichloromethane/methanol (90:10 to 70:30) as mobile phase to give 4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]benzaldehyde (1.55 g, 54%).  
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.60 (m, 2H), 1.72 (m, 2H), 2.07 (m, 2H), 2.15 (s, 3H), 2.22-2.46 (m, 11H), 4.83 (m, 1H), 7.88 (d, J=8.13 Hz, 2H), 8.07 (d, J=8.10 Hz, 2H), 8.21 (s, 1H), 10.11 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=420.2, R<sub>t</sub>=0.70 min.

B. *cis*-1-[4-(4-Methylpiperazino)cyclohexyl]-3-[4-(1,3-oxazol-5-yl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

Sodium methoxide (130 mg, 2.41 mmol) was added in portions to a mixture of 4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzaldehyde (300 mg, 0.715 mmol) in methanol (20 mL). After 5 minutes, (p-tolylsulfonfyl)methyl isocyanide (tosmic) (167 mg, 0.858 mmol) was added in portions. The solution was heated at reflux for 5 hours. Water (10 mL) was added while it was still hot. After cooling on ice for 5 minutes, the solid was filtered and washed with a mixture of methanol/water (50/50, 2 mL) then dried. The filtrate was evaporated to remove organic solvent and the solid was collected and washed with water. The combined solid was first purified by flash column chromatography using dichloromethane/methanol (90:10 to 70:30) as mobile phase then re-crystallized twice from DMF to give *cis*-1-[4-(4-methylpiperazino)cyclohexyl]-3-[4-(1,3-oxazol-5-yl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (90 mg, 27%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.61 (m, 2H), 1.71 (m, 2H), 2.10 (m, 2H), 2.15 (s, 3H), 2.44 (m, 1H), 4.82 (m, 1H), 7.78 (m, 3H), 7.79 (m, 2H), 8.24 (s, 1H), 8.51 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=459.2, R<sub>t</sub>=0.72 min.

20

Example 733: *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide

2,2-Dimethyl-3-phenylpropanoyl chloride (52 mg, 0.264 mmol) was added to a solution of *trans*-3-(4-amino-2-fluoro-5-methoxyphenyl)-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (80 mg, 0.176 mmol) in pyridine (1.5 mL). After 5 hours, the solvent was evaporated and the residue was first purified by flash column chromatography chromatography using dichloromethane/methanol (95:5 to 85:15) as mobile phase then by preparatory LC/MS to give *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide (22 mg, 19%). <sup>1</sup>H NMR (CDCl<sub>3</sub>-*d*) δ 1.33 (s, 6H), 1.57 (m,

30



2H), 1.92 (m, 2H), 2.15 (m, 6H), 2.30 (s, 3H), 2.49 (m, 4H), 2.66 (m, 3H), 2.95 (s, 2H), 3.84 (s, 3H), 4.76 (m, 1H), 5.51 (bs, 2H), 6.98 (d, J=6.86Hz, 1H), 7.15 (m, 2H), 7.23 (m, 3H), 8.01 (s, 1H), 8.35 (s, 1H), 8.47 (d, J=11.88, 1H). LCMS LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=615.3, R<sub>f</sub>=2.18 min.

Example 734: *cis*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)(1H-benzo[d]imidazol-2-yl)methanol

A. 1H-Benzo[d]imidazol-1-ylmethanol

Formaldehyde (37% in water, 1 mL, 13.3 mmol) was added to a solution of 1H-benzo[d]imidazole (1.57 g, 13.3 mmol) in THF (60 ml). After 10 minutes, the solvent was removed and dried to give 1H-benzo[d]imidazol-1-ylmethanol as a brown solid which was used without any further purification. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 5.60 (d, J=7.09Hz, 2H), 6.70 (m, 1H), 7.25 (m, 2H), 7.65 (d, J=9.13Hz, 2H), 8.26 (s, 1H).

B. *cis*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)(1H-benzo[d]imidazol-2-yl)methanol

*n*-Butyllithium (1.34M, 3.0 mL, 4 mmol) was added slowly to a mixture of 1H-benzo[d]imidazol-1-ylmethanol (296 mg, 2.0 mmol) in THF (9.0 mL) at -78°C. The reaction mixture was allowed to warm up to -20°C and kept at -20°C for 30 minutes then cooled back to -78°C. *cis*-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}benzaldehyde (420 mg, 1 mmol) in THF (5 mL) was added slowly. After 20 minutes, the dry ice bath was removed and the reaction mixture was stirred at room temperature overnight. Saturated ammonium chloride solution was added followed by ether. The layers were separated and the aqueous layer was neutralized with sodium hydroxide (1.0N) and extracted with dichloromethane. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated. The residue was first purified by flash column chromatography using dichloromethane/methanol (95:5 to 85:15) as mobile phase then by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min.

(B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give *cis*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)(1*H*-benzo[*d*]imidazol-2-yl)methanol (2 mg, 0.4%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.68 (m, 2H), 1.81 (m, 2H), 2.01 (m, 2H), 2.13 (m, 2H), 2.33 (s, 3H), 2.42 (m, 2H), 2.64 (m, 7H), 4.68 (bs, 3H), 4.93 (m, 1H), 5.77 (bs, 2H), 6.06 (s, 1H), 7.20 (m, 2H), 7.52 (m, 2H), 7.58 (m, 4H), 8.32 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=538.3, R<sub>f</sub>=3.80 min.










10




#### Examples 735-746

Examples 735-746 were prepared from 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde using the following method:

4-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde (50 mg, 0.123 mmol), the appropriate amine (0.246 mmol), sodium triacetoxymethylborohydride (78mg, 0.368 mmol) and glacial acetic acid (32 mg, 0.540 mmol) were mixed in THF (3 mL). After shaking at room temperature overnight on a J-Kem shaker, further amount of the amine (0.246 mmol), sodium triacetoxymethylborohydride (78mg, 0.368 mmol) and glacial acetic acid (32 mg, 0.540 mmol) were added again and the reaction mixtures were shaken at room temperature overnight. The solvent was evaporated and dichloromethane was added followed by sodium hydroxide (1.0N). The layers were separated with the aid of Empore Cartridge. The organic layer was evaporated and the residue was purified by reverse phase preparative LC/MS (Micromass- Column: Hypersil BDS, C18, 5 um, 100x21.2 mm. Eluents: 15% B/A to 100% B/A in 7 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 25 mL/min.). After removing solvent, the resulting solid was dissolved in dichloromethane/sodium hydroxide (1.0N) mixture and the layers were separated. The organic layer was evaporated to give the corresponding product, detailed on the following table.

30

Entry	Structure	Compound name	MH <sup>+</sup>	R <sub>t</sub> (mins)	Qty (mg)
735		2-({4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl}amino)-1-ethanol	453.2	2.05	10
736		2-({4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl}amino)-2-methyl-1-propanol	481.2	2.12	12
737		4-({4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl}amino)-1-butanol	481.2	2.05	10
738		N1-{4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl}-N2,N2-dimethyl-1,2-ethanediamine	480.2	2.03	2
739		1-(4-{[(3-methoxypropyl)amino]methyl}phenyl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine	481.2	2.3	2
740		1-(4-{[(2-methoxyethyl)amino]methyl}phenyl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine	467.2	2.22	10
741		3-(4-phenoxyphenyl)-1-[4-(1,3-thiazolan-3-ylmethyl)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine	481.2	4.2	3
742		2-[{4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl}(2-hydroxyethyl)amino]-1-ethanol	497.2	2.02	2
743		N1-{4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl}-N1,N2,N2-trimethyl-1,2-ethanediamine	494.3	2.47	8

744		1-(4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl)-4-piperidinol	493.3	2.13	2
745		N1-[4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl]-N1,N3,N3-trimethyl-1,3-propanediamine	508.3	1.78	9
746		(1-(4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl)-4-piperidyl)methanol	507.3	2.12	9

Example 747: N1-[4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, dimaleate salt

5

N1-[4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide (380 mg, 0.717 mmol) was dissolved in hot ethyl acetate (70 mL) and maleic acid (167 mg, 1.435 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature for 3 hours. The solid was collected by filtration to give N1-[4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl) benzamide, dimaleate salt (489 mg, 90% ). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.15 (m, 2H), 2.41 (m, 2H), 3.23 (m, 2H), 3.94 (s, 3H), 5.09(m, 1H), 6.14 (m, s, 4H), 7.33 (m, 2H), 7.76 (m, 1H), 7.88 (m, 1H), 7.99 (m, 1H), 8.28 (s, 1H), 8.33 (m, 2H), 8.70 (bs, 1H), 9.92 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=530.2, R<sub>t</sub>=2.03 min.

20 Intermediate 6: N1-4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl-2-fluoro-4-(trifluoromethyl)benzamide

A. *tert*-Butyl 4-[4-amino-3-(4-[2-fluoro-4-(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

2-Fluoro-4-(trifluoromethyl)-1-benzenecarbonyl chloride (3.05 mL, 20.2 mmol) in dichloromethane (25 mL) was added to a solution of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (8.77 g, 20.0 mmol) in pyridine (50 mL) at 0°C. After 5 minutes, the ice water bath was removed and the reaction mixture stirred at room temperature for 1 hours. 2-Fluoro-4-(trifluoromethyl)-1-benzenecarbonyl chloride (0.5 mL, 3.31 mmol) was added and the reaction mixture was stirred for addition 30 minutes. The solvent was evaporated and the residue was dissolved in dichloromethane. The organic layer was washed with water, brine then dried over MgSO<sub>4</sub>. The solvent was evaporated and the residue was purified by flash column chromatography using ethyl acetate/dichloromethane (80:20 to 100:0) as mobile phase to give *tert*-Butyl 4-[4-amino-3-(4-[2-fluoro-4-(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (11.2 g, 89%). <sup>1</sup>H NMR (CDCl<sub>3</sub>-*d*) δ 1.48 (s, 9H), 2.04 (m, 2H), 2.30 (m, 2H), 2.98 (m, 2H), 4.05 (s, 3H), 4.32 (m, 2H), 4.95 (m, 1H), 5.89 (bs, 2H), 7.33 (m, 2H), 7.51 (d, J=11.62 Hz, 1H), 7.61 (d, J=8.21Hz, 1H), 8.36 (m, 2H), 8.72 (d, J=8.18 Hz, 1H), 9.32 (d, J=14.39 Hz, 1H).

B. *N*1-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of trifluoroacetic acid/dichloromethane (20:80, 100 mL) was added to a solution of *tert*-Butyl 4-[4-amino-3-(4-[2-fluoro-4-(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (11.2, 17.79 mmol) in dichloromethane (50 mL) at 0°C. 15 minutes later, the ice-bath was removed and the reaction mixture was stirred at room temperature for 3 hours. The solvents were evaporated and the residue was dissolved in dichloromethane. Saturated sodium bicarbonate solution was added to adjust the pH to about 8. The suspension was lyophilized. Water (100 ml) was added and the aqueous was extracted with dichloromethane repetitively to give *N*1-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-2-

fluoro-4-(trifluoromethyl)benzamide (9.12 g, 97%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.85 (m, 2H), 2.12 (m, 2H), 2.70 (m, 2H), 3.14 (m, 2H), 3.94 (s, 3H), 4.77 (m, 1H), 7.32 (m, 2H), 7.75 (d, J=8.02 Hz, 1H), 7.89 (d, J=10.31Hz, 1H), 8.00 (m, 1H), 8.24 (s, 1H), 8.31 (d, J=8.16 Hz, 1H), 9.90 (s, 1H).

5

#### Examples 748-786








Examples 748-828 were derived from *N*1-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-2-fluoro-4-








(trifluoromethyl)benzamide (Intermediate 6) using method A or method B: Method

- 10 A: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (100 mg, 0.189 mmol), the appropriate aldehyde (0.378 mmol), sodium triacetoxyborohydride (120mg, 0.567 mmol) and glacial acetic acid (48 mg, 0.378 mmol) were mixed in 1,2-dichloroethane (4 mL). After shaking at room temperature overnight, further
- 15 amount of the aldehyde (0.378 mmol), sodium triacetoxyborohydride (120mg, 0.567) and glacial acetic acid (48 mg, 0.378 mmol) were added again and the reaction mixtures were shaken at room temperature overnight. The solvent was evaporated and the residue was purified either by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) or by reverse phase preparative
- 20 HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 μm, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give the corresponding product, detailed on the following table.









- 25 Method B: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (100 mg, 0.189 mmol), the appropriate ketone or some less reactive aldehyde (0.378 mmol), sodium triacetoxyborohydride (120mg, 0.567 mmol) and glacial acetic acid (48 mg, 0.378 mmol) were mixed in 1,2-dichloroethane (4 mL). The reaction mixture was shaken
- 30 at 70°C for 4 hours. The solvent was evaporated and the residue was purified either by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) or by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 μm, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min.









(B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give the corresponding product, detailed on the following table.









	Structure	Compound name	MH <sup>+</sup>	R <sub>t</sub> (mins)	Qty (mg)	Metho d
748		N1-[4-[4-amino-1-(1-ethyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 556.1	2.07	56	A
749		N1-(4-{4-amino-1-[1-(cyclopropylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 582.1	2.22	80	A
750		N1-(4-{4-amino-1-[1-(1H-2-pyrrolylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>+</sup> 607.0	2.45	60	A
751		N1-(4-{4-amino-1-[1-(1H-2-imidazolylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 610.2	2.17	68	B
752		N1-[4-(4-amino-1-[1-[(1-methyl-1H-2-imidazolyl)methyl]-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>+</sup> 622.0	2.23	56	A
753		N1-[4-(4-amino-1-[1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>+</sup> 622.0	2.05	32	A
754		N1-[4-(4-amino-1-[1-[(4-methyl-1H-5-imidazolyl)methyl]-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 622.0	2.08	84	A



		(trifluoromethyl)benzamide, acetate salt				
755		N1-(4-{4-amino-1-[1-(1,3-thiazol-2-ylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 625.1	3.15	73	A
756		N1-{4-[4-amino-1-(1-{[5-(hydroxymethyl)-2-furyl]methyl}-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 638.1	2.20	36	A
757		N1-{4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 542.2	2.03	67	A
758		N1-{4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 570.1	2.08	58	B
759		N1-{4-[4-amino-1-(1-isobutyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>+</sup> 584.0	2.43	54	A
760		N1-(4-{4-amino-1-[1-(2-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 608.1	2.63	82	A
262		N1-(4-{4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 610.2	2.43	54	A



761		<i>N1</i> -(4-{4-amino-1-[1-(1 <i>H</i> -4-imidazolylmethyl)-4-piperidyl]-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>+</sup> 608.0	1.90	55	A
762		<i>N1</i> -(4-{4-amino-1-(1-tetrahydro-2 <i>H</i> -4-pyran-4-yl)-4-piperidyl}-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl)-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 614.2	2.13	91	B
763		<i>tert</i> -butyl 4-{4-[4-amino-3-(4-{[2-fluoro-4-(trifluoromethyl)benzoyl]amino}-3-methoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-1-yl]-1-piperidyl}-1-piperidinecarboxylate	MH <sup>+</sup> 713.3	2.57	74	B
764		<i>N1</i> -(4-{4-amino-1-(1-tetrahydro-3-thiophenyl-4-piperidyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 616.2	2.53	102	B
765		<i>N1</i> -(4-{4-amino-1-(1-benzyl-4-piperidyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 618.0	2.67	69	A
766		<i>N1</i> -(4-{4-amino-1-[1-(2-pyridylmethyl)-4-piperidyl]-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>+</sup> 619.1	2.32	84	A
767		<i>N1</i> -(4-{4-amino-1-[1-(3-pyridylmethyl)-4-piperidyl]-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 619.1	2.32	77	A
768		<i>N1</i> -(4-{4-amino-1-[1-(4-pyridylmethyl)-4-piperidyl]-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 619.1	2.63	81	A

769		<i>N</i> 1-[4-(4-amino-1-{1-[(1-methyl-1H-2-pyrrolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>-</sup> 621.2	2.52	35	B
770		<i>N</i> 1-[4-(4-amino-1-{1-[(5-methyl-2-furyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>-</sup> 622.1	2.65	78	A
771		<i>N</i> 1-(4-{4-amino-1-[1-(2-thienylmethyl)-4-piperidyl]-1H-pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>-</sup> 624.0	3.00	57	B
772		<i>N</i> 1-(4-{4-amino-1-[1-(3-thienylmethyl)-4-piperidyl]-1H-pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>+</sup> 626.2	2.55	87	A
773		<i>N</i> 1-[4-(4-amino-1-{1-[(1-methylpiperidin-4-yl)-4-piperidyl]-1H-pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, diacetate salt	MH <sup>+</sup> 627.2	1.80	72	B
774		<i>N</i> 1-{4-[4-amino-1-(1-tetrahydro-2H-4-thiopyranyl-4-piperidyl)-1H-pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 630.2	2.37	20	B
775		4-({4-[4-amino-3-(4-{[2-fluoro-4-(trifluoromethyl)benzoyl]amino}-3-methoxyphenyl)-1H-pyrazolo[3,4- <i>d</i> ]pyrimidin-1-yl]piperidino)methyl}-1-pyridine-N-oxide	MH <sup>+</sup> 637.2	2.13	93	A
776		<i>N</i> 1-(4-{4-amino-1-[1-(2-fluorobenzyl)-4-piperidyl]-1H-pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 638.2	3.13	84	A

777		N1-(4-{4-amino-1-[1-(3-fluorobenzyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 638.2	3.25	77	A
778		N1-(4-{4-amino-1-[1-(4-fluorobenzyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 638.2	2.87	88	A
779		N1-[4-(4-amino-1-{1-[3-(methylsulfonyl)propyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 618.2	2.42	76	A
780		N1-[4-(4-amino-1-{1-[(5-methyl-2-thienyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 640.2	3.23	73	A
781		N1-(4-{4-amino-1-[1-(3-cyanobenzyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 645.2	3.28	57	A
782		N1-(4-{4-amino-1-[1-(4-cyanobenzyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 645.2	3.32	62	A
783		N1-(4-{4-amino-1-[1-(2-cyanobenzyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 645.2	3.78	62	A
784		N1-(4-{4-amino-1-[1-(4-methoxybenzyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 650.2	2.63	45	A

785		<i>N1</i> -[4-(4-amino-1-[(1-(1-acetyl-piperidin-4-yl)-4-piperidyl]-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide	MH <sup>+</sup> 655.2	2.02	71	B
786		<i>N1</i> -[4-(4-amino-1-[(3-methyl-1 <i>H</i> -4-pyrazolyl)methyl]-4-piperidyl]-1 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH <sup>+</sup> 624.2	2.07	109	A

Example 787: Methyl 2-4-[4-amino-3-(4-[2-fluoro-4-

(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidinoacetate

5

*N1*-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide (122g, 0.230 mmol), methyl 2-bromoacetate (33 uL, 0.346 mmol) and cesium carbonate (150 mg, 0.461 mmol) was mixed with DMF (2 mL). The mixture was heated to 85°C for 2 hours. LC/MS

10

showed formation of two new peaks, one of them was bis-alkylated one and the other the desired product. The crude mixture was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give methyl 2-4-[4-amino-3-(4-[2-fluoro-4-(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidinoacetate (60 mg, 43%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.91 (m, 2H), 2.27 (m, 2H), 2.42 (m, 2H), 2.98 (m, 2H), 3.32 (s, 2H), 3.64 (s, 3H), 3.95 (s, 3H), 4.67 (m, 1H), 7.32 (m, 2H), 7.75 (d, J=7.96Hz, 1H), 7.89 (d, J=10.35 Hz, 1H), 8.00 (s, 1H), 8.24 (s, 1H), 8.30 (d, J=8.13 Hz, 1H), 9.89 (s, 1H). LC/MS

15

(Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=602.2, R<sub>f</sub>=2.80 min.

20

Example 788: *trans*-3-[4-(1*H*-benzo[d]imidazol-1-ylmethyl)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A. 1-(4-Bromobenzyl)-1*H*-benzo[d]imidazole

- 5 1-Bromo-4-(bromomethyl)benzene (2.50 g, 10 mmol), 1*H*-benzo[d]imidazole (1.181 g, 10.0 mmol), potassium hydroxide (0.561 g, 10.0 mmol), potassium carbonate (1.382 g, 10.0 mmol) and tetrabutylammonium bromide (0.161 g, 0.5 mmol) was mixed in xylenes (60 mL). The reaction mixture was heated at 139°C overnight. The hot reaction mixture was filtered and washed with hot
- 10 xylenes. The solvent was evaporated and the residue was purified by flash column chromatography using dichloromethane/methanol (95:5 to 80:20) as mobile phase to give 1-(4-Bromobenzyl)-1*H*-benzo[d]imidazole (1.193 g, 42%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.31 (s, 2H), 7.05 (m, 2H), 7.28 (m, 3H), 7.46 (m, 2H), 7.82 (m, 1H), 7.95 (s, 1H).

- 15 B. 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]-1*H*-benzo[d]imidazole

- A mixture of 1-(4-Bromobenzyl)-1*H*-benzo[d]imidazole (1.193 mg, 4.15 mmol), diboron pinacol ester (1.27 g, 4.98 mmol), [1.1' bis(diphenylphosphino)ferrocene] dichloropalladium (II) complex with
- 20 dichloromethane (1:1) (0.10 g, 0.12 mol) and potassium acetate (1.22 g, 12.46 mol) in *N,N*-dimethylformamide (25 mL) was heated at 85°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. Dichloromethane (20 mL) was added to the residue and the resulting solid was removed by filtration through a pad of celite.
- 25 The filtrate was concentrated and the residue was purified by flash chromatography on silica using dichloromethane/ methanol (98:2 to 95:5) as mobile phase to give 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]-1*H*-benzo[d]imidazole (1.38 g, 100%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.27 (s, 12H), 5.33 (s, 2H), 7.06 (d, J=8.24 Hz, 2H), 7.28 (d, J=8.34 Hz, 2H), 7.84 (d, J=7.70 Hz, 1H), 8.01 (s, 1H).

30

C. *trans*-3-[4-(1*H*-benzo[d]imidazol-1-ylmethyl)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-

## amine

- trans*-3-Iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (200 mg, 0.453 mmol), 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]-1*H*-benzo[*d*]imidazole (303 mg, 0.906 mmol), palladium tetrakis(triphenylphosphine) (0.31 mg, 0.027 mmol) and sodium carbonate (155 mg, 1.09 mmol) were mixed with ethylene glycol dimethyl ether (5 mL) and water (2.5 mL). The reaction mixture was heated at reflux overnight under nitrogen. The solvent was removed and the residue was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8  $\mu$ m, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give *trans*-3-[4-(1*H*-benzo[*d*]imidazol-1-ylmethyl)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (35 mg, 15%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  1.46 (m, 2H), 1.95 (m, 10H), 2.13 (s, (3H), 2.32 (m, 5H), 4.62 (m, 1H), 5.78 (s, 2H), 7.22 (m, 2H), 7.49 (m, 2H), 7.62 (m, 4H), 8.22 (s, 1H), 8.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-Column: Genesis, C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=522.3, R<sub>t</sub>=0.82 min.

20

Example 789: *N*1-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt

- N*1-[4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide (100g, 0.189 mmol), 2-bromoethyl methyl ether (20  $\mu$ L, 0.208 mmol) and potassium carbonate (52 mg, 0.378 mmol) was mixed in DMF (2 mL). The mixture was heated at 65°C overnight. The crude mixture was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8  $\mu$ m, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give *N*1-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt (75 mg, 68%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  1.90

- (m, 2H), 2.22 (m, 4H), 2.54 (m, 2H), 3.02 (m, 2H), 3.26 (s, 3H), 3.46 (m, 2H), 3.94 (m, s, 3H), 4.66 (m, 1H), 7.30 (d, J=8.19Hz, 1H), 7.34 (s, 1H), 7.74 (d, J=7.84Hz, 1H), 7.90 (d, J=10.33Hz, 1H), 7.99 (m, 1H), 8.24 (s, 1H), 8.30 (d, J=8.23 Hz, 1H), 9.89 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-  
5 Column: Genesis, C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=587.2, R<sub>t</sub>=2.17 min.

- Example 790: N1-(4-{4-amino-1-[1-(cyanomethyl)-4-piperidyl]-1H-pyrazolo[3,4-  
10 d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide  
N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (100g, 0.189 mmol), 2-bromoacetonitrile (14  $\mu$ L, 0.208 mmol) and cesium carbonate (52 mg, 0.378 mmol)  
15 was mixed in DMF (2 mL). The mixture was stirred at room temperature overnight. The crude mixture was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8  $\mu$ m, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give, N1-(4-{4-amino-1-[1-(cyanomethyl)-4-piperidyl]-1H-  
20 pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide (68 mg, 64%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.99 (m, 2H), 2.27 (m, 2H), 2.45 (m, 2H), 2.99 (m, 2H), 3.80 (s, 2H), 3.94 (s, 3H), 4.68 (m, 1H), 7.30 (d, J=8.21Hz, 1H), 7.34 (s, 1H), 7.75 (d, J=8.26Hz, 1H), 7.90 (d, J=10.51Hz, 1H), 7.99 (m, 1H), 8.25 (s, 1H), 8.30 (d, J=8.18 Hz, 1H), 9.90 (s, 1H). LCMS (Thermoquest AQA  
25 single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH<sup>+</sup>=569.2, R<sub>t</sub>=3.03 min.

- Example 791: N1-(4-{4-amino-1-[1-(2-amino-2-oxoethyl)-4-piperidyl]-1H-  
30 pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt  
N1-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (100g, 0.189 mmol), 2-

bromoacetamide (28 mg, 0.208 mmol) and cesium carbonate (123 mg, 0.378 mmol) was mixed in DMF (2 mL). The mixture was stirred at room temperature overnight. The crude mixture was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8  $\mu$ m, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give N1-(4-{4-amino-1-[1-(2-amino-2-oxoethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt (70 mg, 63%).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.90 (m, 5H), 2.34 (m, 4H), 2.93 (s, 2H), 2.99 (m, 2H), 3.94 (s, 3H), 4.69 (m, 1H), 7.12 (s, 1H), 7.25 (s, 1H), 7.30 (d, J=8.15Hz, 1H), 7.34 (s, 1H), 7.75 (d, J=8.15Hz, 1H), 7.87 (d, J=10.30Hz, 1H), 7.99 (m, 1H), 8.25 (s, 1H), 8.31 (d, J=8.14 Hz, 1H), 9.90 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.):  $\text{MH}^+$ =587.2,  $R_t$ =2.17 min.

Example 792: 1-(1-methyl-3-piperidyl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine acetate

A solution of racemic 3-iodo-1-(1-methyl-3-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.050 g, 0.00014 mol) in dimethoxyethane (2.5 mL) and water (5 mL) was treated with 4-phenoxyphenylboronic acid (0.033 g, 0.00015 mol), sodium carbonate (0.037 g, 0.00037 mol) and tetrakis (triphenylphosphine) palladium (0) (0.016 g, 0.000014 mol) at 80° C for 18 hours. The organic solvent was removed *in vacuo*, and the crude material was purified by preparative RP-HPLC (Rainin C18, 8  $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give 1-(1-methyl-3-piperidyl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine acetate as a white solid (0.040 g, 0.00009 mol).

$^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.24 (s, 1H), 7.65 (d, 2H), 7.43 (t, 2H), 7.10-7.22 (m, 5H), 4.74-4.84 (m, 1H), 2.94 (dd, 1H), 2.79 (d, 1H), 2.36 (t, 1H), 2.22 (s, 3H), 1.89 (s, 3H), 1.86-2.01 (m, 3H), 1.76-1.84 (m, 1H), 1.60-1.75 (m, 1H);



RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  13.74 min.;  
MS:  $MH^+$  401.

- 5 Example 793: 1-[1-(2-methoxyethyl)-3-piperidyl]-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A solution of racemic 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.050 g, 0.00012 mol) in dimethoxyethane (2.5 mL) and water (5 mL) was treated with 4-phenoxyphenylboronic acid (0.029 g, 0.00014  
10 mol), sodium carbonate (0.033 g, 0.00031 mol) and tetrakis(triphenylphosphine) palladium (0) (0.014 g, 0.00001 mol) at 80° C for 20 hours. The organic solvent was removed *in vacuo*, and the crude material was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in*  
15 *vacuo* and the aqueous mixture was lyophilized to give 1-[1-(2-methoxyethyl)-3-piperidyl]-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.038 g, 0.00007 mol).

$^1H$  NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.24 (s, 1H), 7.65 (d, 2H), 7.43 (t, 2H), 7.09-7.22 (m, 5H), 4.71-4.82 (m, 1H), 3.44 (t, 2H), 3.21 (s, 3H), 3.04 (dd, 1H), 2.91 (d, 1H), 2.47-2.60  
20 (m, 3H), 1.94-2.09 (m, 3H), 1.89 (s, 3H), 1.75-1.84 (m, 1H), 1.57-1.74 (m, 1H);  
RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  14.26 min.;  
MS:  $MH^+$  445.

- 25 Example 794: *Trans* 1-{4-[4-amino-3-(3-chloro-4-{[4-(trifluoromethyl)benzoyl]amino}phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}-4-methylhexahydropyrazinedium dimaleate

A. *Tert*-butyl N-(4-bromo-2-chlorophenyl)carbamate

30 A solution of 4-bromo-2-chloroaniline (5.00 g, 0.0242 mol) in tetrahydrofuran (50 mL) was reacted with a 1.0 M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (53.2 mL, 0.0532 mol). The mixture was stirred 15 minutes at ambient

temperature. Di-*tert*-butyl dicarbonate (6.34 g, 0.0290 mol) was added and the solution was stirred for 2 hours. The solvent was removed *in vacuo*, and the crude material was purified by flash column chromatography on silica using heptane /ethyl acetate (4:1). The solvent was removed *in vacuo* to give *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate as a white solid (4.214 g, 0.0137 mol).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.75 (s, 1H), 7.71 (d, 1H), 7.54 (d, 1H), 7.50 (dd, 1H), 1.46 (s, 9H);

TLC (heptane/ethylacetate 4:1) R<sub>f</sub> 0.54.

10           B.     *Tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate

A mixture of *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate (2.10 g, 0.00685 mol), diboron pinacol ester (2.09 g, 0.00822 mol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.17 g, 0.00021 mol) and potassium acetate (2.02 g, 0.02055 mol) in *N,N*-dimethylformamide (50 ml) was heated at 80°C under a nitrogen atmosphere for 6 hours. The solvent was removed *in vacuo*. The residue was triturated with heptane (70 mL) and the resulting solids were removed by filtration through a pad of Celite ® 521. The heptane was removed *in vacuo* to give *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate as a grey solid (1.93 g, 0.00546 mol):

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.65 (s, 1H), 7.74 (d, 1H), 7.61 (d, 1H), 7.56 (dd, 1H), 1.47 (s, 9H), 1.29 (s, 12H).

25           C.     *Trans tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate

A mixture of *trans* 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.20 g, 0.00498 mol), *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.93 g, 0.00548 mol), sodium carbonate (1.32 g, 0.01245 mol) in 1,2-dimethoxyethane (50 mL) and water (100 mL) was stirred rapidly and tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was added. The reaction mixture was stirred 6 hours at 80°C, after which time additional tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was

added. The reaction mixture was stirred an additional 16 hours at 80°C. The solvents were removed *in vacuo* and the residue was partitioned between ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate (200 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 75 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The product was purified by flash column chromatography on silica using dichloromethane/methanol/ammonium hydroxide (90:10:0.5). The solvent was removed *in vacuo* to give *trans tert-butyl N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate as a white solid (1.993 g, 0.00368 mol):

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.76 (s, 1H), 8.23 (s, 1H), 7.80 (d, 1H), 7.68 (d, 1H), 7.57 (dd, 1H), 4.58-4.71 (m, 1H), 2.15 (s, 3H), 1.89-2.61 (m, 15H), 1.49 (s, 9H), 1.40-1.48 (m, 2H); TLC (dichloromethane/methanol = 90:10) R<sub>f</sub> 0.13, MS: M<sup>+</sup> 541.

- 15 D. *Trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine
- Trans tert-butyl N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate (1.993 g, 0.00368 mol) was added to a solution of 20% trifluoroacetic acid in dichloromethane. The mixture was stirred for 2 hours at ambient temperature. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (50 mL) and washed with a 1.0 M aqueous solution of sodium hydroxide (2 x 25 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to give *trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.564 g, 0.00355 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.45 (d, 1H), 7.31 (dd, 1H), 6.92 (d, 1H), 4.57-4.63 (m, 1H), 2.23-2.55 (m, 9H), 2.14 (s, 3H), 1.89-2.08 (m, 6H), 1.38-1.52 (m, 2H);

TLC (dichloromethane/methanol = 90:10) R<sub>f</sub> 0.08;

- 30 MS: MH<sup>+</sup> 441.

E. *Trans N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-

pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-chlorophenyl)-4-  
(trifluoromethyl)benzamide dimaleate

- To a mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in pyridine (5 mL) at -10° C 4-(trifluoromethyl)-1-benzenecarbonyl chloride (0.188 g, 0.00090 mol) was added dropwise, keeping the temperature below -5° C. The mixture was stirred at -10° C for 15 minutes, and then at ambient temperature for 18 hours. After addition of an 1N aqueous solution of sodium hydroxide (1.0 mL) the mixture was stirred one hour. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate (15 mL) and water (30 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (15 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the purified free base (0.032 g, 0.000052 mol). The free base was dissolved in absolute ethanol (4 mL) and heated to reflux. After addition of a solution of maleic acid (0.018 g, 0.000156mol) in absolute ethanol (1 mL) the solution was refluxed for further 15 minutes. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans* N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-chlorophenyl)-4-(trifluoromethyl)benzamide dimaleate as a white solid (0.020 g, 0.00002 mol):
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 10.42 (s, 1H), 8.26 (s, 1H), 8.20 (d, 2H), 7.96 (d, 2H), 7.80-7.83 (m, 2H), 7.46 (dd, 1H), 6.80-7.20 (b, 2H), 6.13 (s, 4H), 4.61-4.73 (m, 1H), 2.52-2.64 (m, 4H), 2.23-2.46 (m, 5H), 2.16 (s, 3H), 1.90-2.10 (m, 6H), 1.42-1.56 (m, 2H);
- RP-HPLC ( Delta Pak C18, 5µm, 300Å, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.97 min.;
- MS: MH<sup>+</sup> 613.

Example 795: *Trans* N1-(4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-chlorophenyl)-4-(trifluoromethoxy)benzamide dimaleate

- To a mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in pyridine (5 mL) at -10° C 4-(trifluoromethoxy)-1-benzenecarbonyl chloride (0.203 g, 0.00091 mol) was added dropwise, keeping the temperature less than -5° C.
- The mixture was stirred at -10° C for 15 minutes and then at ambient temperature for 18 hours. After addition of an 1*N* aqueous solution of sodium hydroxide (1.0 mL) the mixture was stirred one hour. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate (15 mL) and water (30 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (15 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1*M* ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the purified free base (0.034 g, 0.000054 mol). The free base was dissolved in absolute ethanol (4 mL) and heated to reflux. A solution of maleic acid (0.019 g, 0.000162 mol) in absolute ethanol (1 mL) was added and the solution was refluxed for 15 minutes. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans* N1-(4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-chlorophenyl)-4-(trifluoromethoxy)benzamide dimaleate as a white solid (0.020 g, 0.00002 mol):
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 10.29 (s, 1H), 8.26 (s, 1H), 8.14 (d, 2H), 7.78-7.87 (m, 2H), 7.68 (dd, 1H), 7.57 (d, 2H), 6.80-7.20 (b, 2H), 6.11 (s, 4H), 4.65-4.77 (m, 1H), 2.38-3.60 (m, 12H), 1.95-2.15 (m, 6H), 1.51-1.68 (m, 2H);
- RP-HPLC ( Delta Pak C18, 5μm, 300Å, 15 cm; 5%-85% acetonitrile - 0.1*M* ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 15.41 min.;

MS: MH<sup>+</sup> 629.

Example 796: *Trans* 3-(3-chloro-4-[[5-methyl-2-furyl)methyl]amino]phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in 1,2-dichloroethane (20 mL) was reacted with 5-methyl-2-furfural (0.052 g, 0.00048 mol), acetic acid (0.095 g, 0.00159 mol) and sodium triacetoxymethylborohydride (0.336 g, 0.00159 mol) at ambient temperature. An additional two equivalents of sodium triacetoxymethylborohydride (0.672 g, 0.00318 mol) were added in two 24 hour intervals. The solvents were removed *in vacuo* and the residue was partitioned between chloroform (25 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 25 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *trans* 3-(3-chloro-4-[[5-methyl-2-furyl)methyl]amino]phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.129 g, 0.00022 mol):

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.51 (d, 1H), 7.39 (dd, 1H), 6.93 (d, 1H), 6.20 (d, 1H), 6.14 (t, 1H), 5.98 (d, 1H), 4.55-4.66 (m, 1H), 4.38 (d, 2H), 2.23 (s, 3H), 2.18-2.61 (m, 10 H), 2.14 (s, 3H), 1.91 (s, 3H), 1.87-2.09 (m, 5H), 1.37-1.53 (m, 2H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.48 min;

MS: MH<sup>+</sup> 535.

Example 797: *Trans* 3-{3-chloro-4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-

## amine acetate

- A mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in 1,2-dichloroethane (20 mL) was reacted with 2-chloro-6-fluorobenzaldehyde (0.076 g, 0.00048 mol), acetic acid (0.095 g, 0.00159 mol) and sodium triacetoxymethylborohydride (0.336 g, 0.00159 mol) at ambient temperature. An additional three equivalents of sodium triacetoxymethylborohydride (1.008 g, 0.00477 mol) were added in three 24 hour intervals, after which time all the starting material had been consumed. The solvents were removed *in vacuo* and the residue was partitioned between chloroform (25 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 25 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give to give *trans*-3-{3-chloro-4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.074 g, 0.00011 mol):
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 8.20 (s, 1H), 7.52 (d, 1H), 7.35-7.47 (m, 4H), 6.99 (d, 1H), 5.75 (t, 1H), 4.55-4.66 (m, 1H), 4.57 (d, 2H), 2.25-2.61 (m, 11 H), 2.16 (s, 3H), 1.91 (s, 3H), 1.87-2.09 (m, 4H), 1.37-1.53 (m, 2H);
- RP-HPLC ( Delta Pak C18, 5µm, 300Å, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 15.97 min.;
- MS: MH<sup>+</sup> 583.

Example 798: *Trans* N1-(4-{4-amino-1-[1-(1*H*-2-imidazolylcarbonyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide maleate

- A mixture of N1-[4-{4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-phenyl-1-cyclopropanecarboxamide (0.200 g, 0.00041 mol) in toluene (10 mL) was reacted with 5*H*,10*H*-diimidazo[1,5-*α*:1,5-*d'*]pyrazine-

- 5,10-dione (0.040 g, 0.00021 mol) at reflux for 18 hours. An additional equivalent of 5*H*,10*H*-diimidazo[1,5-*a*:1,5-*d'*]pyrazine-5,10-dione was added and the mixture was refluxed an additional 6 hours. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the free base (0.103 g, 0.00017 mol). The free base was dissolved in absolute ethanol (10 mL) and heated to reflux. After addition of a solution of maleic acid (0.030 g, 0.00034 mol) in absolute ethanol (1 mL) the solution was refluxed for 15 minutes, after which time a precipitate formed. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans* N1-(4-{4-amino-1-[1-(1*H*-2-imidazolylcarbonyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide maleate as a white solid (0.055 g, 0.00008 mol):
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.63 (s, 1H), 8.26 (s, 1H), 8.22 (d, 1H), 8.00 (b, 1H), 7.74 (b, 1H), 7.43-7.48 (m, 1H), 7.16-7.33(m, 7H), 6.21 (s, 2H), 4.97-5.13 (m, 1H), 2.91-3.47 (m, 4H), 2.53-2.65 (m, 1H), 2.30-2.45 (m, 1H), 2.07-2.26 (m, 2H), 1.95-2.07 (m, 2H), 1.45-1.50 (m, 1H), 1.28-1.32 (m, 1H);
- RP-HPLC ( Delta Pak C18, 5 $\mu$ m, 300Å, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.17 min.; MS: MH<sup>+</sup> 578.
- Example 799: *Cis* N1-(4-{4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide acetate
- A. *Cis* N1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide
- A mixture of *cis* N1-{4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-2-phenylcyclopropane-1-carboxamide (0.605 g, 0.0012 mol), lithium perchlorate (0.189 g, 0.0018 mol) and potassium cyanide (0.116 g, 0.0018 mol) in acetonitrile (60 ml) was heated at 80°C



for two days. Cooled to ambient temperature, diluted with water (30 mL) and extracted with diethyl ether (3x 30 mL). The combined organic phases were dried over magnesium sulfate. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica using

- 5 dichloromethane/methanol (95:5). The solvent was removed *in vacuo* to give *cis* N1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide as a white solid (0.602 g, 0.0011 mol):

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.64 (s, 1H), 8.23 (t, 2H), 7.31 (t, 2H), 7.25 (s, 1H),  
 10 7.17- (m, 4H), 4.61-4.62 (m, 1H), 3.91 (s, 1H), 2.66 (s, 2H), 2.55-2.62 (m, 1H), 2.31-2.45 (m, 3H), 1.58-1.89 (m, 6H), 1.45-1.53 (m, 1H), 1.28-1.38 (m, 1H);  
 RP-HPLC ( Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 15.21 min.;  
 MS: MH<sup>+</sup> 538.

15

- B. *Cis* N1-(4-{4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide acetate

- To a solution of *cis* N1-(4-{4-amino-1-[4-(cyanomethyl)-4-  
 20 hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropane-carboxamide (0.200 g, 0.00037 mol) in methanol (20 ml) and ammonium hydroxide (1 mL) Raney nickel (0.5 mL) was added. The mixture was stirred 18 hours under a hydrogen atmosphere (1 atm). The reaction mixture was filtered through celite and the solvent was removed *in vacuo*. The residue was  
 25 purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *Cis* N1-(4-{4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-  
 30 cyclopropanecarboxamide acetate as a white solid (0.045 g, 0.000083 mol).:  
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.64 (s, 1H), 8.23 (d, 1H), 8.22-8.24 (m, 1H), 7.17-7.33 (m, 7H), 4.65-4.67 (m, 1H), 3.91 (s, 3H), 2.84-2.91 (m, 1H), 2.53-2.55

(m, 1H), 2.33-2.40 (m, 4H), 1.85 (s, 3H), 1.35-1.80 (m, 9H), 1.30-1.33 (m, 1H);  
RP-HPLC ( Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M  
ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.29 min.;

MS: MH<sup>+</sup> 444

5

Example 800: *Cis* N1-(4-{4-amino-1-[4-(2-amino-2-oxoethyl)-4-  
hydroxycyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-  
methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide

To a well-stirred solution of *cis* N1-(4-{4-amino-1-[4-(cyanomethyl)-4-  
10 hydroxycyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-(trans)-  
2-phenyl-1-cyclopropanecarboxamide (0.200 g, 0.00037 mol) in dimethylsulfoxide  
(4 mL) potassium carbonate (0.216 g, 0.00156 mol) was added at ambient  
temperature. A 30% aqueous solution of hydrogen peroxide (0.6 mL) was added  
15 dropwise, keeping the temperature constant. The mixture was stirred at ambient  
temperature for 32 hours. Water (20 mL) was added to the mixture, and the  
precipitate which formed was filtered. The precipitate was washed with water and  
dried *in vacuo*. The solid was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m,  
300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M  
20 ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo*  
and the aqueous mixture was lyophilized to give *cis* N1-(4-{4-amino-1-[4-(2-  
amino-2-oxoethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-  
methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide as a white solid  
(0.117 g, 0.00021 mol):

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.64 (s, 1H), 8.23 (d, 1H), 8.22 (s, 1H), 7.43-7.48  
25 (m, 1H), 7.15-7.35 (m, 7H), 7.05-7.10 (m, 1H), 4.97 (s, 1H), 4.61-4.71 (m, 1H), 3.91  
(s, 3H), 2.54-2.64 (m, 1H), 2.30-2.44 (m, 3H), 2.24 (s, 2H), 1.55-1.81 (m, 6H), 1.45-  
1.53 (m, 1H), 1.28-1.36 (m, 1H);

RP-HPLC ( Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M  
ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.05 min.;

30 MS: MH<sup>+</sup> 556.

Example 801: *Cis* N1-[4-(4-amino-1-{4-[(dimethylamino)methyl]-4-

hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(*trans*)-2-phenyl-1-cyclopropanecarboxamide acetate

- To a solution of *cis* N1-[4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-(*trans*)-2-phenylcyclopropane-1-carboxamide (0.190 g, 0.000302 mol) in 2-propanol (10 mL) a 2 M solution of dimethylamine in methanol (0.91 mL) was added and the resulting mixture was heated at 65° C in a pressure tube for 18 hours. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *Cis* N1-[4-(4-amino-1-[4-[(dimethylamino)methyl]-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(*trans*)-2-phenyl-1-cyclopropanecarboxamide acetate as a white solid (0.109 g, 0.000177 mol):
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.64 (s, 1H), 8.23 (d, 1H), 8.22-8.24 (m, 1H), 7.17-7.33 (m, 7H), 4.56-4.68 (m, 1H), 3.91 (s, 3H), 2.54-2.64 (m, 1H), 2.30-2.44 (m, 3H), 2.28 (s, 6H), 2.24 (s, 2H), 1.91 (s, 3H), 1.63-1.78 (m, 4H), 1.44-1.58 (m, 3H), 1.28-1.36 (m, 1H); RP-HPLC (Delta Pak C18, 5µm, 300Å, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.54 min.; MS: MH<sup>+</sup> 556.

- Example 802: *Trans* N2-(4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(2*R*)tetrahydro-1*H*-2-pyrrolecarboxamide acetate

- A solution of *trans* 3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00046 mol) in *N,N*-dimethylformamide (10 mL) was reacted with 1-hydroxy-7-azabenzotriazole (0.068 g, 0.00050 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.132 g, 0.00069 mol), D-Boc-proline (0.108 g, 0.00050 mol) and *N,N*-diisopropylethylamine (0.184 g, 0.00142 mol) at ambient temperature for 24 hours. The solvent was removed *in vacuo* and the residue was

- partitioned between dichloromethane (10 mL) and a 5% aqueous citric acid solution (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (15 mL) and dried over magnesium sulfate.
- 5 The solvent was removed *in vacuo* and the residue was stirred in 20% trifluoroacetic acid in dichloromethane for 6 hours at ambient temperature. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 Å, 25 cm; 5% isocratic for five minutes, then 5%-40% acetonitrile - 0.1M ammonium acetate over 20 min, 21 mL/min). The acetonitrile was removed *in*
- 10 *vacuo* and the aqueous mixture was lyophilized to give *trans* N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(2*R*)tetrahydro-1*H*-2-pyrrolicarboxamide acetate (0.096 g, 0.00016 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.33 (s, 1H), 8.45 (d, 1H), 8.22 (s, 1H), 7.25 (s, 1H), 7.21 (d, 1H), 4.58-4.69 (m, 1H), 3.93 (s, 3H), 3.77 (dd, 1H), 2.96-3.04 (m, 1H), 2.74-2.84 (m, 1H), 2.47-2.58 (m, 5H), 2.23-2.45 (m, 5H), 2.14 (s, 3H), 1.91 (s, 3H), 1.88-2.11 (m, 7H), 1.78-1.88 (m, 1H), 1.60-1.69 (m, 2H), 1.39-1.54 (m, 2H);
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300Å, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 8.47 min.;
- 20 MS: MH<sup>+</sup> 534.

- Example 803: 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate
- A. 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate
- 25 A solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.00 g, 0.019 mol) in *N,N*-dimethylformamide (50 mL) was reacted with 60% sodium hydride in oil (0.92 g, 0.023 mol) at ambient temperature. The mixture was stirred for 15 minutes, and 4-nitropyridine-*N*-oxide (5.37 g, 0.038 mol) was added. The mixture was heated at 100° C. for 18 hours. The precipitate which formed was filtered,
- 30 washing with *N,N*-dimethylformamide and ethyl acetate to give 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate (3.79 g, 0.011 mol) as a tan solid:

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.38 (s, 1H), 8.34 (d, 2H), 8.24 (d, 2H);  
RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R<sub>t</sub> 7.36 min.;  
MS: MH<sup>+</sup> 355.

5

B. 4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate

A suspension of 4-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate (0.140 g, 0.00040 mol) in dimethoxyethane (7 mL) and water (15 mL) was reacted with 4-phenoxyphenylboronic acid (0.093 g, 0.00043 mol), sodium carbonate (0.105 g, 0.00099 mol) and tetrakis(triphenylphosphine) palladium (0) (0.046 g, 0.00004 mol) at 80° C for 18 hours. The solid was filtered to give 4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.138 g, 0.00035 mol) as a brown solid. A portion (0.040 g, 0.00010 mol) was purified by preparative RP-HPLC (Rainin C18, 8 $\mu$ m, 300 A, 25 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the product 4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate as a white solid (0.013 g, 0.00003 mol).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.44 (s, 1H), 8.34-8.41 (m, 4H), 7.77 (d, 2H), 7.45 (t, 2H), 7.13-7.24 (m, 5H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.66 min.;

MS: MH<sup>+</sup> 397.

Example 804: 3-(4-phenoxyphenyl)-1-(4-pyridyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.100 g, 0.00025 mol) and 10% palladium on carbon (0.016 g, 0.00002 mol) in acetic acid (3 mL) was reacted with sodium hypophosphite monohydrate (0.033 g, 0.00038 mol) at 60° C. After 2 hours, an

- additional 10% palladium on carbon (0.016 g, 0.00002 mol) was added. The mixture was stirred 18 hours after which time additional 10% palladium on carbon (0.016 g, 0.00002 mol) and sodium hypophosphite monohydrate (0.033 g, 0.00038 mol) was added. The mixture was stirred for an additional 24 hours. The mixture was filtered through Celite ® 521, washing with acetic acid. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 Å, 25 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 ml/min). The acetonitrile was removed in *vacuo* and the aqueous mixture was lyophilized to give 3-(4-phenoxyphenyl)-1-(4-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.020 g, 0.00005 mol) as a white solid:
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.71 (d, 2H), 8.46 (s, 1H), 8.39 (dd, 2H), 7.78 (d, 2H), 7.46 (t, 2H), 7.13-7.25 (m, 5H);
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300Å, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 17.31 min.;
- MS: MH<sup>+</sup> 381.

- Example 805: *N*2-{4-[4-amino-1-(4-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-2-indolecarboxamide
- A. *N*2-{4-[4-amino-1-(4-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-2-indolecarboxamide
- A suspension of 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyridinium iodide (0.500 g, 0.0014 mol) in dimethoxyethane (15 mL) and water (30 mL) was reacted with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1H-2-indolecarboxamide (0.631 g, 0.00155 mol), sodium carbonate (0.374 g, 0.0035 mol) and tetrakis(triphenylphosphine) palladium (0) (0.163 g, 0.00014 mol) at 80° C for 18 hours. The solid was filtered and washed with water. The solid was slurried in ethyl acetate for 18 hours and filtered, washing with ethyl acetate. The solid was dried *in vacuo* to give crude 4-[4-amino-3-(3-methoxy-4-[(1-methyl-1H-2-indolyl)-carbonyl]aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-pyridinium iodate (0.523 g, 0.0010 mol) as a brown solid:
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300Å, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 10 min, 1mL/min) R<sub>t</sub> 10.92 min.;

MS: MH<sup>+</sup> 507.

B. *N*2-[4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

- 5 A suspension of 4-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)carbonyl]amino) phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.200 g, 0.00039 mol) and 10% palladium on carbon (0.042 g, 0.00004 mol) in acetic acid (3 mL) was reacted with sodium hypophosphite monohydrate (0.063 g, 0.00059 mol) at 60° C for 2 hours. Additional 10% palladium
- 10 on carbon (0.042 g, 0.00004 mol) and sodium hypophosphite (0.045 g, 0.00042 mol) was added and the mixture was stirred for 24 hours. The solvent was removed *in vacuo* and the residue was slurried in methanol for 4 hours. The mixture was filtered through Celite ® 521, washing with methanol. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 A, 25
- 15 cm; 50% isocratic for five minutes, then 50%-100% acetonitrile - 0.1M ammonium acetate over 25 min, 21 ml/min). The acetonitrile was removed in *vacuo* and the aqueous mixture was lyophilized to give *N*2-[4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.020 g, 0.00004 mol) as a white solid:
- 20 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.48 (s, 1H) 8.72 (d, 2H), 8.47 (s, 1H), 8.42 (d, 2H), 8.20 (d, 1H), 7.72 (d, 1H), 7.60 (d, 1H), 7.48 (s, 1H), 7.42 (d, 1H), 7.36 (s, 1H) 7.34 (t, 1H), 7.16 (t, 1H), 4.05 (s, 3H), 3.99 (s, 1H);
- RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 19.50 min.;
- 25 MS: MH<sup>+</sup> 491.

Example 806: 1-(6-amino-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine; and

- Example 807: 3-(4-phenoxyphenyl)-1-(2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine
- 30

A solution of 3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00079 mol) in *N*-methyl pyrrolidinone (10 mL) was reacted with 60% sodium hydride in oil (0.032 g, 0.00079 mol). After gas evolution ceased, the

- mixture was stirred at ambient temperature for 30 minutes, and 5-bromo-2-nitropyridine (0.161 g, 0.00079 mol) was added and heated at 40° C for 18 hours. Additional 60% sodium hydride in oil (0.032 g, 0.00079 mol) was added and the mixture was stirred an additional 2 hours. The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane (15 mL) and water (25 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organics were washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica using heptane/ethyl acetate (1:2) as an eluent to give two products. The less polar compound, 1-(6-nitro-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was suspended in absolute ethanol (10 mL) and *N,N*-dimethylformamide (5 mL) and 10% palladium on carbon (0.007 g) was added. The mixture was stirred under a balloon atmosphere of hydrogen for 18 hours. The mixture was filtered through pad of Celite ® 521, washing with absolute ethanol. The solvent was removed *in vacuo* to give 1-(6-amino-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.007 g, 0.00002 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.53 (d, 1H) 8.31 (s, 1H), 7.97 (dd, 1H), 7.73 (d, 2H), 7.44 (t, 2H), 7.12-23 (m, 5H), 6.60 (d, 1H), 6.20 (s, 2H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 15.38 min.; MS: MH<sup>+</sup> 396.

- The more polar compound, 3-(4-phenoxyphenyl)-1-(5-bromo-2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was suspended in absolute ethanol (10 mL) and *N,N*-dimethylformamide (5 mL) and 10% palladium on carbon (0.007 g) was added. The mixture was stirred under a balloon atmosphere of hydrogen for 18 hours. The mixture was filtered through pad of Celite ® 521, washing with absolute ethanol. The solvent was removed *in vacuo* to give 3-(4-phenoxyphenyl)-1-(2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.030 g, 0.00007 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.60-8.64 (m, 1H) 8.37 (s, 1H), 8.20 (d, 1H), 8.03-8.08 (m, 1H), 7.76 (d, 2H), 7.41-7.49 (m, 3H), 7.12-7.23 (m, 5H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 16.32 min.;



MS:  $\text{MH}^+$  381.

A general procedure for reductive amination with *trans*-3-(4-amino-phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and an aldehyde as starting materials is given below. Examples 808 and 809 were prepared using this method.

Protocol:

A mixture of *trans*-3-(4-amino-phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1 eq.), the corresponding aldehyde (1.05 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, quenched with saturated solution of sodium bicarbonate in water and concentrated again. The residue was purified by preparative HPLC (Hypersil C18, 8 $\mu\text{m}$ , 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired products. Example 808 was prepared according to this method using the aldehyde 2-methoxy-3-formylpyridine and Example 809 was prepared using the aldehyde 2-formyl-indole.

Example 808: *trans*-3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-[4-(4-methyl-piperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400MHz)  $\delta$  8.18 (s, 1H), 8.06 (dd, 1H), 7.61 (d, 1H), 7.35 (d, 2H), 6.95 (dd, 1H), 6.69 (d, 2H), 6.51 (t, 1H), 4.60 (m, 1H), 4.26 (d, 2H), 3.94 (s, 3H), 2.64 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H); RP-HPLC (Delta Pak C18, 5 $\mu\text{m}$ , 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  12.07 min.

MS:  $\text{MH}^+$  528.

Example 809: *trans*-3-[4-[(1*H*-2-indolyl)methyl]amino]phenyl]-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  11.08 (s, 1H), 8.19 (s, 1H), 7.44 (d, 1H), 7.36 (d, 2H), 7.32 (d, 1H), 7.01 (t, 1H), 6.95 (t, 1H), 6.81 (d, 2H), 6.47 (t, 1H), 6.35 (s, 1H), 4.60 (m, 1H), 4.45 (d, 2H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

- 5 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.74 min.

MS: MH<sup>+</sup> 536.

- Example 810: *Trans*-3-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)methyl]-1,2-dihydro-2-pyridinone diacetate

- Trans*-3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.105 g, 0.000199mol) was dissolved in 30% hydrogen bromide in acetic acid (4 mL) and the mixture was refluxed for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)methyl]-1,2-dihydro-2-pyridinone diacetate (0.0204 g, 0.0000324 mol) as a white solid.

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.18 (s, 1H), 7.29 (m, 4H), 6.68 (d, 2H), 6.40 (t, 1H), 6.15 (m, 1H), 4.60 (m, 1H), 4.09 (d, 2H), 2.64 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 9.40 min. MS: MH<sup>+</sup> 514.

- A general procedure for reductive amination with *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine and an aldehyde as starting materials is given below.
- Examples 811-813 were prepared using this method.

Protocol :

A mixture of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4- (1 eq.), the corresponding aldehyde (1.05 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, quenched with saturated solution of sodium bicarbonate in water and concentrated again. The residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired products.

Example 811 was prepared using the aldehyde 2-amino-4-chloro-5-formyl-1,3-thiazole. Example 812 was prepared using the aldehyde 5-methyl-3-formyl-isoxazole. Example 813 was prepared using the aldehyde 4-formyl-1,3-thiazole.

Example 811: *Trans*-5-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyanilino)methyl]-4-chloro-1,3-thiazol-2-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.19 (s, 2H), 7.06 (m, 3H), 6.68 (d, 1H), 5.76 (t, 1H), 4.60 (m, 1H), 4.30 (d, 2H), 3.85 (s, 3H), 2.6-2.2 (br, 9H), 2.17 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.59 min.  
MS: MH<sup>+</sup> 583.

Example 812: *Trans*-3-(3-methoxy-4-[(5-methyl-3-isoxazolyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.04 (m, 2H), 6.68 (d, 1H), 6.16 (s, 1H), 5.86 (t, 1H), 4.60 (m, 1H), 4.37 (d, 2H), 3.86 (s, 3H), 2.6-2.2 (br, 9H), 2.40 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.53 min.  
MS: MH<sup>+</sup> 532.

Example 813: *Trans*-3-{3-methoxy-4-[(1,3-thiazol-4-ylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

- 5 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.08 (s, 1H), 8.19 (s, 1H), 7.47 (s, 1H), 7.06 (s, 1H), 7.03 (d, 1H), 6.68 (d, 1H), 5.76 (t, 1H), 4.60 (m, 1H), 4.52 (d, 2H), 3.88 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);  
RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.17 min.  
10 MS: MH<sup>+</sup> 534.

A general procedure for the synthesis of benzotetrahydrofuran-derivatives with *trans*- 3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and the appropriate 2-hydroxy-benzaldehyde as starting material is given below. Examples 814 and 815 were prepared using this  
15 method.

Protocol:

- Trans*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1 equiv., 0.0001–0.0002 mol scale) and the  
20 corresponding 2-hydroxy-benzaldehyde (1 equiv.) were combined in absolute ethanol (5 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was concentrated under reduced pressure and the residue dried overnight to yield the corresponding imine, which was used without further purification.  
Trimethylsulfoxonium iodide (2.5 equiv.) was dissolved in anhydrous  
25 dimethylsulfoxide (2 mL) and a 60% dispersion of sodium hydride in paraffine (2.5 equiv.) was added at once. After 10 min., the solution of the imine in anhydrous dimethylsulfoxide (2 mL) was added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 2.5 hours. The solution was poured into ice-cold water (50 mL) and extracted with dichloromethane (2x40  
30 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25

min, 21 mL/min) to yield the final compound.

Example 814 was prepared using 2-hydroxy-4,6-dichlorobenzaldehyde and Example 815 was prepared using 2-hydroxy-4-chlorobenzaldehyde.

- 5 Example 814: *Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.39 (d, 2H), 7.14 (s, 1H), 7.07 (s, 1H), 6.80 (d, 2H), 6.56 (d, 1H), 5.34 (m, 1H), 4.80 (dd, 1H), 4.60 (m, 1H), 4.42 (dd, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
- 10 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 16.03 min.
- MS: MH<sup>+</sup> 593.
- 15 Example 815: *Trans*-3-{4-[(4-chloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.39 (d, 2H), 7.28 (t, 1H), 6.99 (d, 1H), 6.89 (d, 1H), 6.81 (d, 2H), 6.53 (d, 1H), 5.34 (m, 1H), 4.74 (dd, 1H), 4.60 (m, 1H), 4.38 (dd, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
- 20 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.42 min.
- MS: MH<sup>+</sup> 559.
- 25 Example 816: *Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]-3-methoxyphenyl-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
- Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]-3-methoxyphenyl-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate was prepared using the method of Examples 814 and 815 using *trans*- 3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and 2-hydroxy-

4,6-dichlorobenzaldehyde as the starting materials.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.11 (m, 4H), 6.80 (d, 1H), 5.45(m, 2H), 4.84 (dd, 1H), 4.60 (m, 1H), 4.42 (dd, 1H), 3.82 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

- 5 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 16.85 min.  
MS: MH<sup>+</sup> 623.

Intermediate 7: *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

A. *tert*-butyl 4-[4-amino-3-(4-[(benzyloxy)carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

- A mixture of benzyl *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (9.54 g, 0.027 mol), *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (10.0 g, 0.0225 mol), tetrakis-(triphenylphosphine)palladium (1.56 g, 0.00135 mol) and sodium carbonate (5.97 g, 0.0563 mol) was heated in a mixture of ethylene glycol dimethyl ether (120 mL) and water (60 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was partitioned between water (150 mL) and dichloromethane (150 mL); the organic phase was washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was triturated in diethyl ether and the precipitate was collected by filtration and dried to yield *tert*-butyl 4-[4-amino-3-(4-[(benzyloxy)carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (10.1 g, 0.0186 mol) as a white solid.

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.00 (s, 1H), 8.23 (s, 1H), 7.64 (d, 2H), 7.43 (d, 2H), 7.36 (m, 5H), 5.18 (s, 2H), 4.90 (m, 1H), 4.08 (br, 2H), 3.00 (br, 2H), 2.02 (m, 4H), 1.42 (s, 9H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 18.58 min.

B. *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

To a solution of *tert*-butyl 4-[4-amino-3-(4-

- 5 [(benzyloxy)carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (5.0 g, 0.0092 mol) in tetrahydrofuran (150 mL) 10% palladium on carbon (1.0 g) was added and the reaction mixture was hydrogenated on a Parr shaker over 96 hours. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was
- 10 triturated in *n*-heptane and the precipitate was collected by filtration and dried to yield *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (2.51 g, 0.0061 mol) as an off-white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.20 (s, 1H), 7.35 (d, 2H), 6.69 (d, 2H), 5.42 (s, 2H), 4.90 (m, 1H), 4.08 (br, 2H), 3.00 (br, 2H), 2.02 (m, 4H), 1.42 (s, 9H);
- 15 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.18 min.

- Examples 817-829 were prepared with the following general procedure for reductive amination followed by BOC deprotection. *Tert*-butyl 4-[4-amino-3-(4-
- 20 aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate and the appropriate aldehyde were used as starting materials.

Protocol:

- A mixture of *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (1 eq.), aldehyde (1.2 eq.), sodium
- 25 triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, triturated in ethyl acetate and treated with with a 4*N* aqueous solution of hydrochloric acid. The resulting mixture was stirred for 1 hour; aqueous phase was
- 30 neutralized with saturated solution of sodium bicarbonate in water and the layers separated. Organic phase was concentrated under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile

– 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired products.

The following compounds were made using the above procedure:

Example 817: 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.57 (d, 1H), 7.53 (d, 1H), 7.39 (d, 2H), 7.23 (m, 2H), 6.85 (d, 2H), 6.80 (s, 1H), 6.66 (t, 1H), 4.70 (m, 1H), 4.51 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

10 ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.37 min.

MS: MH<sup>+</sup> 440.

Example 818: 3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

15 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 8.06 (d, 1H), 7.61 (d, 1H), 7.36 (d, 2H), 6.96 (dd, 1H), 6.69 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.27 (d, 2H), 3.94 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.06 min.

20 MS: MH<sup>+</sup> 431.

Example 819: 3-(4-[(5-methyl-2-thienyl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

25 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.36 (d, 2H), 6.85 (d, 1H), 6.77 (d, 2H), 6.64 (d, 1H), 6.54 (t, 1H), 4.70 (m, 1H), 4.41 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.38 (s, 3H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.85 min.

MS: MH<sup>+</sup> 420.

30

Example 820: 3-{4-[(2-furylmethyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate



$^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.19 (s, 1H), 7.59 (s, 1H), 7.36 (d, 2H), 6.77 (d, 2H), 6.46 (t, 1H), 6.39 (d, 1H), 6.34 (d, 1H), 4.70 (m, 1H), 4.31 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

5 ammonium acetate over 20 min, 1mL/min)  $R_t$  10.96 min.

MS:  $\text{MH}^+$  390.

Example 821: 3-[4-(benzylamino)phenyl]-1-(4-piperidyl)-1H-pyrazolo[3,4-  
d]pyrimidin-4-amine diacetate

10  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.19 (s, 1H), 7.34 (m, 6H), 7.24 (t, 1H), 6.73 (d, 2H), 6.60 (t, 1H), 4.70 (m, 1H), 4.33 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 20 min, 1mL/min)  $R_t$  12.32 min.

15 MS:  $\text{MH}^+$  400.

Example 822: 3-[4-[(2-methoxybenzyl)amino]phenyl]-1-(4-piperidyl)-1H-  
pyrazolo[3,4-d]pyrimidin-4-amine diacetate

20  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.19 (s, 1H), 7.35 (d, 2H), 7.24 (m, 2H), 7.01 (d, 1H), 6.90 (t, 1H), 6.70 (d, 2H), 6.41 (t, 1H), 4.70 (m, 1H), 4.28 (d, 2H), 3.85 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 20 min, 1mL/min)  $R_t$  12.73 min.

MS:  $\text{MH}^+$  430.

25

Example 823: 3-[4-[(3-methoxybenzyl)amino]phenyl]-1-(4-piperidyl)-1H-  
pyrazolo[3,4-d]pyrimidin-4-amine diacetate

30  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.19 (s, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 6.96 (m, 2H), 6.81 (d, 1H), 6.72 (d, 2H), 6.59 (t, 1H), 4.70 (m, 1H), 4.30 (d, 2H), 3.74 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 20 min, 1mL/min)  $R_t$  12.38 min.

MS:  $\text{MH}^+$  430.

Example 824: 3-{4-[(4-methoxybenzyl)amino]phenyl}-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

5  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.35 (m, 4H), 6.90 (d, 2H), 6.72 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.25 (d, 2H), 3.73 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) *R*<sub>t</sub> 12.37 min.

10 MS:  $\text{MH}^+$  430.

Example 825: 1-(4-piperidyl)-3-(4-[3-(trifluoromethyl)benzyl]aminophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

15  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.71 (m, 2H), 7.58 (m, 2H), 7.36 (d, 2H), 6.72 (m, 3H), 4.70 (m, 1H), 4.44 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) *R*<sub>t</sub> 14.08 min.

MS:  $\text{MH}^+$  468.

20

Example 826: 1-(4-piperidyl)-3-(4-[4-(trifluoromethyl)benzyl]aminophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

25  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.70 (d, 2H), 7.60 (d, 2H), 7.36 (d, 2H), 6.72 (m, 3H), 4.70 (m, 1H), 4.44 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) *R*<sub>t</sub> 14.23 min.

MS:  $\text{MH}^+$  468.

30 Example 827: 3-(4-[(2-methyl-1,3-thiazol-4-yl)methyl]aminophenyl)-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

$^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.41 (d, 2H), 7.26 (s, 1H), 6.73 (d,

2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.36 (d, 2H), 3.07 (m, 2H), 2.70 (s, 3H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  10.13 min.

5 MS:  $MH^+$  421.

Example 828: 3-{4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine diacetate

$^1H$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.19 (s, 1H), 7.42 (m, 4H), 7.26 (t, 1H), 6.83 (d, 10 2H), 6.27 (t, 1H), 4.72 (m, 1H), 4.37 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  12.32 min.

MS:  $MH^+$  452.

15

Example 829: 3-(4-[2-fluoro-4-(trifluoromethyl)benzyl]aminophenyl)-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine diacetate

$^1H$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  8.19 (s, 1H), 7.61 (m, 3H), 7.38 (d, 2H), 6.73 (d, 2H), 6.68 (t, 1H), 4.70 (m, 1H), 4.47 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 20 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  12.83 min.

MS:  $MH^+$  486.

25 Example 830: 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]-3-methoxyphenyl}-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine diacetate

A mixture of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinecarboxylate (g, mol), benzofuran-2-carbaldehyde (0.046 g, 0.000315 mol), sodium triacetoxyborohydride (0.089 g, 30 0.00042 mol.) and acetic acid (0.024 mL, 0.00042 mol) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, triturated in ethyl acetate (4mL) and treated with a 4N aqueous solution of

- hydrochloric acid (1 mL). The resulting mixture was stirred for 1 hour; aqueous phase was neutralized with saturated solution of sodium bicarbonate in water and the layers separated. The organic phase was concentrated under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]-3-methoxyphenyl}-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.027 g, 0.0000457 mol).
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.55 (m, 2H), 7.22 (m, 2H), 7.06 (m, 2H), 6.80 (d, 1H), 6.75 (s, 1H), 5.80 (t, 1H), 4.70 (m, 1H), 4.57 (d, 2H), 3.89 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 14.83 min.
- MS: MH<sup>+</sup> 470.
- 15 Example 831: 3-[4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)phenyl]-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
- Salicylaldehyde (0.063 g, 0.000513 mol) and *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.200 g, 0.000489 mol) were combined in absolute ethanol (5 mL) and stirred at ambient
- 20 temperature for 48 hours. The reaction mixture was concentrated under reduced pressure and the residue dried overnight to yield *tert*-butyl 4-[4-amino-3-(4-{[1-(2-hydroxyphenyl)methylidene]amino}phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate which was used without further purification.
- Trimethylsulfoxonium iodide (0.269 g, 0.00122 mol) was dissolved in anhydrous
- 25 dimethylsulfoxide (2 mL) and a 60% dispersion of sodium hydride in paraffine (0.049 g, 0.00122 mol) was added at once. After 10 min., the solution of *tert*-butyl 4-[4-amino-3-(4-{[1-(2-hydroxyphenyl)methylidene]amino}phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate in anhydrous dimethylsulfoxide (2 mL) was added and the resulting mixture was stirred at ambient temperature under an
- 30 atmosphere of nitrogen for 2.5 hours. The solution was poured into ice-cold water (70 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure

to yield crude *tert*-butyl 4-[4-amino-3-[4-(2,3-dihydrobenzo[b]furan-3-ylamino)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinecarboxylate which was used without further purification. The crude compound was dissolved in ethyl acetate (5 mL) and treated with a 4N aqueous solution of hydrochloric acid (1.5 mL).

- 5 The resulting emulsion was vigorously stirred for 1 hour; the water layer was neutralized with saturated solution of sodium bicarbonate in water and the layers were separated. The organic phase was concentrated under reduced pressure and residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield 3-[4-(2,3-
- 10 dihydrobenzo[b]furan-3-ylamino)phenyl]-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine acetate (0.038g, 0.000078 mol) as a white solid
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.19 (s, 1H), 7.41 (m, 3H), 7.25 (t, 1H), 6.89 (m, 4H), 6.51 (t, 1H), 5.35 (m, 1H), 4.79 (m, 2H), 4.27 (m, 1H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 3H), 1.79 (m, 2H);
- 15 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.38 min.
- MS: MH<sup>+</sup> 428.

- Example 832: *Trans*-3-(4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-
- 20 pyrazolo[3,4-d]pyrimidin-3-yl]anilino)-1H-1 $\lambda$ <sup>6</sup>-benzo[d]isothiazole-1,1-dione acetate

A. 3-chloro-1H-1 $\lambda$ <sup>6</sup>-benzo[d]isothiazole-1,1-dione

- Saccharin (10.0 g, 0.0546 mol) and phosphorus pentachloride (12.6 g,
- 25 0.060mol) were heated at 170°C for 1.5 hours. The reaction mixture was cooled to ambient temperature and suspended in diethyl ether (200 mL). The precipitate was collected by filtration, thoroughly washed with diethyl ether and dried to yield 3-chloro-1H-1 $\lambda$ <sup>6</sup>-benzo[d]isothiazole-1,1-dione (3.7 g, 0.0184 mol) as a white solid which was used without further purification.
- 30 MS: MH<sup>+</sup> 202.

B. 3-(4-bromoanilino)-1H-1 $\lambda$ <sup>6</sup>-benzo[d]isothiazole-1,1-dione

To a solution of 3-chloro-1*H*-1 $\lambda^6$ -benzo[*d*]isothiazole-1,1-dione (1.0 g, 0.00496 mol) in acetone (20 mL), 4-bromoaniline (1.71 g, 0.00992 mol) was added at once and the mixture was stirred for 15 min. The mixture was concentrated under reduced pressure and the residue was suspended in water (100 mL). The precipitate was collected by filtration, thoroughly washed with water and dried to yield 3-(4-bromoanilino)-1*H*-1 $\lambda^6$ -benzo[*d*]isothiazole-1,1-dione (1.57 g, 0.00467 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.93 (s, 1H), 8.47 (d, 1H), 8.09 (d, 1H), 7.93 (m, 4H), 7.69 (d, 2H);

C. 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1 $\lambda^6$ -benzo[*d*] isothiazole-1,1-dione

A mixture of 3-(4-bromoanilino)-1*H*-1 $\lambda^6$ -benzo[*d*]isothiazole-1,1-dione (1.57 g, 0.00467 mol), diboron pinacol ester (1.43 g, 0.00561 mol), [1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.114 g, 0.00014 mol) and potassium acetate (1.37 g, 0.014 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was triturated in diethyl ether to yield 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1 $\lambda^6$ -benzo[*d*] isothiazole-1,1-dione (1.14 g, 0.00297 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.92 (br, 1H), 8.51 (d, 1H), 8.08 (d, 1H), 7.91 (m, 4H), 7.68 (d, 2H), 1.29 (s, 12H).

D. *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1 $\lambda^6$ -benzo[*d*]isothiazole-1,1-dione acetate

A mixture of 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1 $\lambda^6$ -benzo[*d*] isothiazole-1,1-dione (0.09 g, 0.000234 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.08 g,

- 0.00018 mol), tetrakis-(triphenylphosphine)palladium (0.013 g, 0.000011 mol) and sodium carbonate (0.048 g, 0.00045 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1H-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione acetate (0.075 g, 0.000119 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 8.29 (d, 1H), 8.23 (s, 1H), 7.91 (m, 3H), 7.79 (m, 2H), 7.66 (d, 2H), 4.65 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
- RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.27 min.
- MS: MH<sup>+</sup> 572.

- Example 833: *Cis*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1H-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione diacetate
- Cis*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1H-1λ<sup>6</sup>-benzo[*d*]isothiazole-1,1-dione diacetate was prepared from 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1H-1λ<sup>6</sup>-benzo[*d*] isothiazole-1,1-dione (0.09 g, 0.000234 mol) and *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine by a similar protocol as described above.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 8.42 (d, 1H), 8.23 (s, 1H), 7.91 (m, 3H), 7.84 (m, 2H), 7.62 (d, 2H), 4.80 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.07 (m, 4H), 1.91 (s, 6H), 1.65(m, 2H), 1.58 (m, 2H);
- RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.59 min.
- MS: MH<sup>+</sup> 572.

Example 835: *Trans-N3*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine acetate

A. *N*1-(4-bromophenyl)-2-fluorobenzamide

- 5 A solution of 2-fluorobenzoyl chloride (5.82 g, 0.0367 mol) and 4-bromoaniline (6.31 g, 0.0367 mol) in anhydrous dichloromethane (150 mL) was cooled to 0°C and *N,N*-diisopropylethylamine (5.21 g, 0.0407 mol) was added under nitrogen atmosphere dropwise. The resulting mixture was stirred at ambient temperature for 24 hours, concentrated and the residue partitioned between ethyl acetate (120 mL) and water (100 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold diethyl ether (50 mL) and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluorobenzamide (9.6 g, 0.0326 mol) as a white solid.
- 10 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.54 (s, 1H), 7.66 (m, 3H), 7.56 (m, 3H), 7.34 (m, 2H).

TLC (ethyl acetate / heptane 1:2) R<sub>f</sub> 0.37

B. *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide

- A mixture of *N*1-(4-bromophenyl)-2-fluorobenzamide (3.3 g, 0.0112 mol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphctane-2,4-disulfide (2.27 g, 0.00561 mol) was heated in toluene at reflux under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica using ethyl acetate/*n*-heptane (1:6) as mobile phase to yield *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (3.1 g, 0.010 mol) as a yellow solid.
- 20 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  12.13 (s, 1H), 7.93 (d, 2H), 7.62 (m, 3H), 7.51 (m, 1H), 7.31 (m, 2H).

TLC (ethyl acetate / heptane 1:4) R<sub>f</sub> 0.27

30

C. *N*1-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime

A mixture of *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (1.56



g, 0.00505 mol), hydroxylamine hydrochloride (0.44 g, 0.00631 mol) and sodium bicarbonate (0.53 g, 0.00631 mol) was heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue  
5 partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold diethyl ether and the precipitate was collected by filtration and dried to yield N1-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime (1.21 g, 0.00392 mol) as an off-white solid.  
10 solid.  
TLC (ethyl acetate / heptane 1:4) R<sub>f</sub> 0.12

D. *N*-benzo[d]isoxazol-3-yl-*N*-(4-bromophenyl)amine

To a solution of N1-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime (1.51 g,  
15 0.00489 mol) in *N*-methylpyrrolidinone (25 mL), potassium *tert*-butoxide (0.54 g, 0.00513 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and  
20 ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate/ *n*-heptane (1:5) as mobile phase to yield *N*-benzo[d]isoxazol-3-yl-*N*-(4-bromophenyl)amine (0.95 g, 0.00329 mol) as a white solid.  
25 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.72 (s, 1H), 8.13 (d, 1H), 7.68 (d, 2H), 7.61 (m, 2H), 7.54 (d, 2H), 7.37 (dd, 1H).  
TLC (ethyl acetate / heptane 1:4) R<sub>f</sub> 0.26

E. *N*-benzo[d]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-3-yl)phenyl]amine  
30

A mixture of *N*-benzo[d]isoxazol-3-yl-*N*-(4-bromophenyl)amine (1.30 g, 0.0045 mol), diboron pinacol ester (1.37 g, 0.0054 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with

- dichloromethane (1:1) (0.110 g, 0.000135 mol) and potassium acetate (1.32 g, 0.0135 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ *n*-heptane (1:5) as mobile phase to yield *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.40 g, 0.00119 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.74 (s, 1H), 8.16 (d, 1H), 7.70 (m, 4H), 7.61 (d, 2H), 7.37 (dd, 1H), 1.29 (s, 12H).
- TLC (ethyl acetate / heptane 1:4) R<sub>f</sub> 0.21

- F. *Trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine acetate

- A mixture of *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.10 g, 0.000298 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.101 g, 0.000229 mol), tetrakis-(triphenylphosphine)palladium (0.016 g, 0.0000137 mol) and sodium carbonate (0.061 g, 0.000573 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine acetate (0.102 g, 0.000175 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.81 (s, 1H), 8.23 (s, 1H), 8.19 (d, 1H), 7.88 (d, 2H), 7.65 (m, 4H), 7.40 (m, 1H), 4.65 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium

acetate over 20 min, 1mL/min) R<sub>t</sub> 13.66 min.

MS: MH<sup>+</sup> 524.

Example 836: *Cis-N3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)benzo[d]isoxazol-3-amine diacetate*

*Cis-N3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)benzo[d]isoxazol-3-amine diacetate* was prepared from *N-benzo[d]isoxazol-3-yl-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine* and *cis-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine* by a similar protocol as described above.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.86 (s, 1H), 8.26 (s, 1H), 8.24 (d, 1H), 7.93 (d, 2H), 7.67 (m, 4H), 7.43 (m, 1H), 4.83 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.08 (m, 4H), 1.91 (s, 6H), 1.74 (m, 2H), 1.62 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 13.77 min.

MS: MH<sup>+</sup> 524.

Example 837: *N3-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}benzo[d]isoxazol-3-amine acetate*

A mixture of *N-benzo[d]isoxazol-3-yl-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine* (0.087 g, 0.000258 mol), *tert*-butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboxylate (0.088 g, 0.000198 mol), tetrakis-(triphenylphosphine)palladium (0.014 g, 0.000012 mol) and sodium carbonate (0.053 g, 0.000495 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure and the residue partitioned between water and dichloromethane. The organic phase was dried with magnesium sulfate and concentrated under reduced pressure to yield crude *tert*-butyl 4-{4-amino-3-[4-(benzo[d]isoxazol-3-ylamino)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-1-piperidinecarboxylate which was used without further purification.

- It was dissolved in ethyl acetate (5 mL) and treated with a 4N aqueous solution of hydrochloric acid (1 mL). The resulting emulsion was vigorously stirred for 1 hour; the water layer was neutralized with saturated solution of sodium bicarbonate in water and the layers were separated. The organic phase was concentrated under reduced pressure and residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *N*3-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}benzo[*d*]isoxazol-3-amine acetate (0.009g, 0.0000185 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.82 (s, 1H), 8.20 (m, 2H), 7.89 (d, 2H), 7.65 (m, 4H), 7.41 (t, 1H), 4.74 (m, 1H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 3H), 1.79 (m, 2H);
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 11.20 min.
- MS: MH<sup>+</sup> 427.

- Example 838: *Trans*-3-[4-(1H-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
- A. *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide
- N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (1.50 g, 0.00485 mol) and a 1M solution of hydrazine in tetrahydrofuran (6.3 mL, 0.0063 mol) were heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. Additional 3 mL of a 1M solution of hydrazine in tetrahydrofuran was added and the stirring at reflux was continued for another 6 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated to yield *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide (1.54 g, 0.0050 mol) as a tan solid.
- TLC (ethyl acetate / heptane 1:3) R<sub>f</sub> 0.10

B. *N*-(4-bromophenyl)-*N*-(1H-3-indazolyl)amine

To a solution of *N*-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide (1.2 g, 0.00391 mol) in *N*-methyl pyrrolidinone (25 mL), potassium *tert*-butoxide (0.50 g, 0.0041 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate/ *n*-heptane (1:5) as mobile phase to yield *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine (0.29 g, 0.0010 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  12.06 (s, 1H), 9.03 (s, 1H), 7.93 (d, 1H), 7.65 (d, 2H), 7.35 (m, 4H), 7.03 (dd, 1H).

TLC (ethyl acetate / heptane 1:3) R<sub>f</sub> 0.26

C. *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine

A mixture of *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine (0.29 g, 0.00101 mol), diboron pinacol ester (0.31 g, 0.00121 mol), [1.1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.025 g, 0.00003 mol) and potassium acetate (0.294 g, 0.003 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ *n*-heptane (1:3) as mobile phase to yield *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.064 g, 0.000191 mol) as an off-white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  12.09 (s, 1H), 9.06 (s, 1H), 7.94 (d, 1H), 7.64 (d, 2H), 7.57 (d, 2H), 7.35 (m, 2H), 7.03 (dd, 1H), 1.28 (s, 12H).

TLC (ethyl acetate / heptane 1:3) R<sub>f</sub> 0.21

D. *Trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A mixture of *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-

- 5 dioxaborolan-2-yl)phenyl]amine (0.064 g, 0.000191 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.070 g, 0.000159 mol), tetrakis-(triphenylphosphine)palladium (0.011 g, 0.0000095 mol) and sodium carbonate (0.042 g, 0.000398 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80°C for 16 hours under an
- 10 atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-
- 15 *d*]pyrimidin-4-amine acetate (0.035 g, 0.000060 mol) as a white solid.
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 12.09 (s, 1H), 9.14 (s, 1H), 8.21 (s, 1H), 7.99 (d, 1H), 7.83 (d, 2H), 7.55 (d, 2H), 7.37 (m, 2H), 7.06 (t, 1H), 4.64 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.49 (m, 2H);
- RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>t</sub> 12.96 min.
- MS: MH<sup>+</sup> 523.

Example 839: *Trans*-*N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-

- 25 (trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate

A. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide

- A solution of 2-fluoro-4-(trifluoromethyl)benzoyl chloride (5.05 g, 0.0223 mol) and 4-bromoaniline (3.83 g, 0.0223 mol) in anhydrous dichloromethane (150 mL) was cooled to 0°C and *N,N*-diisopropylethylamine (4.26 mL, 0.0245 mol) was
- 30 added under nitrogen atmosphere dropwise. The resulting mixture was stirred at ambient temperature for 24 hours, concentrated and the residue was partitioned between ethyl acetate (120 mL) and water (100 mL). The organic phase was washed

with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold n-heptane (50 mL) and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide (7.1 g, 0.0196 mol) as a white solid.

- 5  $^1\text{H NMR}$  (DMSO- $d_6$ , 400MHz)  $\delta$  10.74 (s, 1H), 7.90 (m, 2H), 7.74 (d, 1H), 7.68 (d, 2H), 7.56 (d, 2H).

B. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide

- 10 A mixture of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide (7.1 g, 0.0196 mol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (3.97 g, 0.0098 mol) was heated in toluene at reflux under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was
- 15 purified by flash chromatography on silica using ethyl acetate/n-heptane (1:8) as mobile phase to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide (6.0 g, 0.0159 mol) as a yellow solid.

$^1\text{H NMR}$  (DMSO- $d_6$ , 400MHz)  $\delta$  12.33 (s, 1H), 7.94 (d, 2H), 7.81 (m, 2H), 7.65 (m, 3H).

- 20 TLC (ethyl acetate / heptane 1:4)  $R_f$  0.61

C. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime

- A mixture of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide (2.50 g, 0.00663 mol), hydroxylamine hydrochloride (0.65 g, 0.00928 mol) and sodium bicarbonate (0.78 g, 0.00928 mol) was heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium
- 30 bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold n-heptane and the precipitate was collected by filtration and dried

to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime (2.35 g, 0.00625 mol) as an off-white solid.

TLC (ethyl acetate / heptane 1:4)  $R_f$  0.12

5           D.     *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine

To a solution of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime (2.25 g, 0.00598 mol) in *N*-methylpyrrolidinone (30 mL), potassium *tert*-butoxide (0.71 g, 0.00628 mol) was added and the resulting solution  
10 was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was  
15 washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold *n*-heptane and the precipitate was collected by filtration and dried to yield *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine (1.75 g, 0.0049 mol) as an off-white solid.

$^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  9.95 (s, 1H), 8.37 (d, 1H), 8.14 (s, 1H), 7.78 (d, 1H), 7.68 (d, 2H), 7.58 (d, 2H).

20     TLC (ethyl acetate / heptane 1:5)  $R_f$  0.31

E.     *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine

A mixture of *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[d]isoxazol-3-yl]amine (1.75 g, 0.0049 mol), diboron pinacol ester (1.49 g, 0.0059 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with  
25 dichloromethane (1:1) (0.120 g, 0.000147 mol) and potassium acetate (1.44 g, 0.0144 mol) in *N,N*-dimethylformamide (10 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient  
30 temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ *n*-heptane (1:6) as



mobile phase to yield *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (0.065 g, 0.000161 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.97 (s, 1H), 8.39 (d, 1H), 8.14 (s, 1H), 7.77 (d, 1H), 7.71 (s, 4H), 1.29 (s, 12H).

F. *Trans-N3*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate

A mixture of *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (0.062 g, 0.000153 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.065 g, 0.000146 mol), tetrakis-(triphenylphosphine)palladium (0.010 g, 0.000087 mol) and sodium carbonate (0.039 g, 0.000365 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 $\mu$ m, 25 cm; 10-70% acetonitrile – 0.1M ammonium acetate over 30 min, 21mL/min) to yield *trans-N3*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate (0.026 g, 0.0000398 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.05 (s, 1H), 8.44 (d, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.88 (d, 2H), 7.79 (d, 1H), 7.69 (d, 2H), 4.67 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R<sub>f</sub> 16.18 min.

MS: MH<sup>+</sup> 592.

Example 840: *N2*-[4-(4-amino-1-{1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide, dimaleate salt

A. *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

- 3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, HCl salt (6.75 g, 17.73 mmol), *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (7.571 g, 18.63 mmol), palladium tetrakis(triphenylphosphine) (1.23 g, 1.06 mmol) and sodium carbonate (8.27 g, 78.03 mmol) were mixed with ethylene glycol dimethyl ether (180 mL) and water (90 mL). The reaction mixture was heated at reflux overnight. Organic solvent was removed under reduced pressure and the aqueous suspension was extracted with copious dichloromethane. The combined organic layer was washed with water then brine, dried over MgSO<sub>4</sub>, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol/ammonium hydroxide (90:10:0.5 to 60:40:0.5) as mobile phase to give *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (4.38 g). The aqueous suspension was filtered, washed with water and dried to give *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (2.77 g). Combined the solids (7.15 g, 81%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.85 (m, 2H), 2.08 (m, 2H), 2.64 (m, 2H), 3.10 (m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.77 (m, 1H), 7.13 (m, 1H), 7.33 (m, 4H), 7.58 (d, J=8.45 Hz, 1H), 7.71 (d, J=7.94 Hz, 1H), 8.12 (d, J=8.15 Hz, 1H), 8.25 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R<sub>T</sub>=1.97 min. MH<sup>+</sup>= 497.3.

25

B. *N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

- N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol), 2-methyl-1*H*-4-imidazolecarbaldehyde (83 mg, 0.755 mmol), sodium triacetoxymethylborohydride (159 mg, 0.755 mmol) and glacial acetic acid (30 mg, 0.554 mmol) were mixed in 1,2-dichloroethane (6 mL). The reaction mixture was stirred

- at room temperature overnight. Saturated sodium bicarbonate solution was added to adjust the pH to about 8. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over  $\text{MgSO}_4$ , filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol/ammonium hydroxide (95:5:0.5 to 80:20:05) as mobile phase to give *N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (215 mg, 72%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.91 (m, 2H), 2.23 (m, 7H), 3.00(m, 2H), 3.41 (s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.78 (m, 1H), 6.72 (s, 1H), 7.15 (m, 1H), 7.32 (m, 4H), 7.78 (d,  $J=8.43$  Hz, 1H), 7.70 (d,  $J=7.92$  Hz, 1H), 8.11 (d,  $J=7.92$  Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3  $\mu\text{m}$ , 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.):  $R_T=2.00$  min.  $\text{MH}^+=591.3$ .

- C. *N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt
- N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (210 mg, 0.355 mmol) was dissolved in hot ethyl acetate (25 mL) and a few drops of ethanol. Maleic acid (83mg, 0.711 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature for 3 hours. The solid was collected by filtration to give *N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt (255 mg, 87%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  2.12 (m, 2H), 2.43 (m, 5H), 2.92 (m, 2H), 3.38 (m, 2H), 3.96 (s, 3H), 3.99 (s, 2H), 4.04 (s, 3H), 4.93 (m, 1H), 6.13 (s, 4H), 7.16 (m, 1H), 7.34 (m, 5H), 7.60 (d,  $J=8.43$  Hz, 1H), 7.70 (d,  $J=7.92$  Hz, 1H), 7.72 (d,  $J=8.15$  Hz, 1H), 8.27 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3  $\mu\text{m}$ , 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5

min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.):  
R<sub>T</sub>=1.98 min. MH<sup>+</sup>= 591.3.

Example 841: N2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-  
pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1*H*-2-  
indolecarboxamide, dimaleate salt

A. N2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-  
pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1*H*-2-  
indolecarboxamide, diacetate salt

10 N2-(4-{4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-  
methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol), 1*H*-4-  
imidazolecarbaldehyde (73 mg, 0.755 mmol), sodium triacetoxyborohydride (159  
mg, 0.755 mmol) and glacial acetic acid (30 mg, 0.554 mmol) were mixed in 1,2-  
dichloroethane (6 mL). The reaction mixture was stirred at room temperature  
15 overnight. Saturated sodium bicarbonate solution was added to adjust the pH to  
about 8. The layers were separated and the aqueous layer was extracted with  
dichloromethane. The combined organic layer was washed with brine, dried over  
MgSO<sub>4</sub>, filtered and evaporated. The residue was first purified by flash column  
chromatography using dichloromethane/methanol/ammonium hydroxide (95:5:0.5 to  
20 80:20:05) as mobile phase then purified again by reverse phase preparative HPLC  
using acetonitrile/water (50mM ammonium acetate buffer) as mobile phase to give  
N2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-  
*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, diacetate  
salt (170 mg, 49%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.90 (m, 8H), 2.20 (m, 4H), 2.99 (m,  
25 2H), 3.47(s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.67 (m, 1H), 7.15 (m, 1H), 7.31 (m,  
5H), 7.54 (s, 1H), 7.58 (d, J=8.43 Hz, 1H), 7.70 (d, J=7.95 Hz, 1H), 8.10 (d, J=8.14  
Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS,  
Finnigan HPLC- Column: Genesis, C18, 3 μm, 33x4.6 mm. Eluents: 30% B/A to  
95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5),  
30 0.8 mL/min.): R<sub>T</sub>=1.97 min. MH<sup>+</sup>= 577.3.

B. N2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-  
pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1*H*-2-

indolecarboxamide, dimaleate salt

- N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, diacetate salt (170 mg, 0.244 mmol) was dissolved in hot ethyl acetate (25 mL) and a few drops of ethanol. Maleic acid (103mg, 0.884 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature for 3 hours. The solid was collected by filtration to give *N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt (153 mg, 76%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.19 (m, 2H), 2.49 (m, 2H), 3.19 (m, 2H), 3.52 (m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.21 (s, 2H), 5.02 (m, 1H), 6.15 (s, 4H), 7.16 (m, 1H), 7.32 (m, 5H), 7.40 (s, 1H), 7.59 (d, J=8.45 Hz, 1H), 7.71 (d, J=7.95 Hz, 1H), 7.98 (bs, 1H), 8.13 (d, J=8.16 Hz, 1H), 8.27 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R<sub>T</sub>=1.98 min. MH<sup>+</sup>= 577.3.

- Example 842: *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt
- A. *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

- N*2-(4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol), 1-bromo-2-fluoroethane (47 ul, 0.629 mmol), Potassium carbonate (87 mg, 0.629 mmol) and Sodium iodide (10 mg, 0.066 mmol) were mixed in DMF (3 mL). The reaction mixture was heated at 80°C overnight. The crude reaction mixture was purified by reverse phase preparative HPLC using acetonitrile/water (50mM ammonium acetate buffer) as mobile phase to give *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (221 mg, 81%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.91 (m,

- 2H), 2.26 (m, 4H), 2.66 (m, 1H), 2.73 (m, 1H), 3.05 (m, 2H), 3.97 (s, 3H), 4.04 (s, 3H), 4.61 (m, 1H), 4.61 (m, 1H), 4.64 (m, 1H), 7.15 (m, 1H), 7.33 (m, 4H), 7.58 (d, J=8.46 Hz, 1H), 7.70 (d, J=7.95 Hz, 1H), 8.11 (d, J=8.14 Hz, 1H), 8.25 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.):  $R_t$ =2.17 min.  $MH^+$ = 543.3.
- 5

- B. *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt
- 10

- N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (221 mg, 0.407 mmol) was dissolved in hot ethyl acetate (25 mL) and a few drops of ethanol.
- 15
- Maleic acid (94mg, 0.814 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature overnight. No precipitate was formed. The organic solvent was removed and the solid was triturated with ethyl acetate. The solid was collected by filtration to give *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt (252 mg, 80%).  $^1H$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$  2.34 (m, 2H), 2.54 (m, 2H), 3.49-3.67(m, 6H), 3.96 (s, 3H), 4.04 (s, 3H), 4.81 (m, 1H), 4.92 (m, 1H), 5.06 (m, 1H), 6.14 (s, 4H), 7.16 (m, 1H), 7.34 (m, 4H), 7.60 (d, J=8.32 Hz, 1H), 7.70 (d, J=7.95 Hz, 1H), 8.14 (d, J=8.15 Hz, 1H), 8.29 (s, 1H), 9.45 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis,
- 25
- C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.):  $R_t$ =2.17 min.  $MH^+$ = 543.3.

- Example 843: *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt
- 30

- A. *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-

## indolecarboxamide

- N*2-(4-{4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol), 2-bromo-1,1-difluoroethane (91 mg, 0.629 mmol), Potassium carbonate (87 mg, 0.629 mmol) and Sodium iodide (10 mg, 0.066 mmol) were mixed in DMF (3 mL). The reaction mixture was heated at 80°C overnight. HPLC showed only about fifty percent conversion. The bath temperature was lowered to 55°C and more 2-bromo-1,1-difluoroethane (0.1 mL) was added. After stirring at 55°C overnight, more 2-bromo-1,1-difluoroethane (0.1 mL) was added and the reaction mixture was stirred at 55°C overnight. HPLC showed most of starting material was converted to product. The crude reaction mixture was purified by reverse phase preparative HPLC using acetonitrile/water (50mM ammonium acetate buffer) as mobile phase to give *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (227 mg, 81%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.89 (m, 2H), 2.27 (m, 2H), 2.42 (m, 2H), 2.80 (m, 1H), 3.05 (m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.69 (m, 1H), 6.17 (t, J=55.81 Hz, J=4.35 Hz, 1H), 7.15 (m, 1H), 7.33 (m, 4H), 7.78 (d, J=7.94 Hz, 1H), 7.70 (d, J=7.94 Hz, 1H), 8.11 (d, J=8.19 Hz, 1H), 8.25 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R<sub>T</sub>=3.32 min. MH<sup>+</sup>= 561.3.

- B. *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt

- N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (227 mg, 0.405 mmol) was dissolved in hot ethyl acetate (25 mL). Maleic acid (94 mg, 0.810 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature overnight. No precipitate was formed. After stirring at room temperature for 4 days, precipitate was formed at bottom of the flask. The solvent was decanted. The solid was washed with ethyl acetate and dried to give *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-

- methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt (220 mg, 68 %).
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.05 (m, 2H), 2.40 (m, 2H), 2.84-3.32 (bm, 6H), 3.96 (s, 3H), 4.04 (s, 3H), 4.85 (m, 1H), 6.22 (s, 4H), 6.34 (t, J=56.07 Hz, 1H), 7.15 (m, 1H), 7.33 (m, 4H), 7.59 (d, J=8.45 Hz, 1H), 7.70 (d, J=7.94 Hz, 1H), 8.12 (d, J=8.19 Hz, 1H), 8.28 (s, 1H), 9.45 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R<sub>T</sub>=3.32 min. MH<sup>+</sup>= 561.3.
- 10 Example 844: *N*2-[4-[4-amino-1-(1-ethyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide
- N*2-[4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol),
- 15 acetaldehyde (44 mg, 1.007 mmol) and sodium triacetoxyborohydride (212 mg, 1.007 mmol) were mixed in 1,2-dichloroethane (6 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was purified by reverse phase preparative HPLC using acetonitrile/water (50mM ammonium acetate buffer) as mobile phase to give *N*2-[4-[4-amino-1-(1-ethyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (247 mg, 93%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.04 (t, J=7.15 Hz, 3H), 1.92 (m, 2H), 2.08 (m, 2H), 2.25 (m, 2H), 2.40 (q, J=7.15 Hz, 2H), 3.03 (m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.68 (m, 1H), 7.13 (m, 1H), 7.33 (m, 4H), 7.58 (d, J=8.00Hz, 1H), 7.70 (d, J=7.95 Hz, 1H), 8.11 (d, J=8.15 Hz, 1H), 8.25 (s, 1H), 9.44
- 20 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R<sub>T</sub>=2.08 min. MH<sup>+</sup>= 525.3.
- 25
- 30 Examples 845- were made using the methods described in Example 844.
- Example 845: *N*2-[4-(4-amino-1-{1-[(3-methyl-1*H*-4-pyrazolyl)methyl]-4-



piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide, Acetate salt

Yield: 187 mg, 63%

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.91 (m, 2H), 2.09 (m, 2H), 2.19 (m, 5H), 2.96 (m, 2H), 3.35 (s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.67 (m, 1H), 7.17 (m, 1H), 7.31 (m, 5H), 7.58 (d, J=8.46 Hz, 1H), 7.70 (d, J=7.94 Hz, 1H), 8.10 (d, J=8.15 Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R<sub>T</sub>=2.03 min. MH<sup>+</sup>= 591.3.

Example 846: N<sup>2</sup>-(4-{4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide Yield 233 mg, 80%

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.91 (m, 2H), 2.13-2.23 (m, 4H), 3.00 (m, 2H), 3.39 (s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.68 (m, 1H), 6.47 (s, 1H), 7.31 (m, 4H), 7.60 (m, 3H), 7.70 (d, J=7.94 Hz, 1H), 8.11 (d, J=8.05 Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R<sub>T</sub>=2.37 min. MH<sup>+</sup>= 577.3.

Example 847: N<sup>2</sup>-(4-[4-amino-1-(1-tetrahydro-2*H*-4-pyran-4-yl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

- The reaction was carried out at 70°C overnight instead of room temperature overnight as described in the example 844.

Yield 176 mg, 71%.

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.46(m, 2H), 1.71 (m, 2H), 1.91 (m, 2H), 2.20 (m, 2H), 2.30 (m, 2H), 3.07 (m, 3H), 3.27 (m, 2H), 3.91(m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.67 (m, 1H), 7.15 (m, 1H), 7.33 (m, 4H), 7.58 (d, J=8.44 Hz, 1H), 7.70 (d, J=7.94 Hz, 1H), 8.10 (d, J=8.04 Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm, 33x4.6 mm.

Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.):  $R_T=2.08$  min.  $MH^+=581.3$ .

Example 848: *N*2-(4-{4-amino-1-[(1-acetyl)piperidin-4-yl]-piperidin-4-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

The reaction was carried out at 70°C overnight instead of room temperature overnight as described in the Example 844.

Yield 223 mg, 71%.

- 10  $^1H$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$  1.28 (m, 1H), 1.43 (m, 1H), 1.75 (m, 2H), 1.91 (m, 2H), 1.99 (s, 3H), 2.19 (m, 2H), 2.34 (m, 2H), 2.54 (m, 2H), 3.01 (m, 3H), 3.83 (m, 1H), 3.96 (s, 3H), 4.04 (s, 3H), 4.38 (m, 1H), 4.66 (m, 1H), 7.15 (m, 1H), 7.31 (m, 4H), 7.78 (d,  $J=7.94$  Hz, 1H), 7.70 (d,  $J=7.94$  Hz, 1H), 8.11 (d,  $J=8.15$  Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-  
15 Column: Genesis, C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.):  $R_T=1.97$  min.  $MH^+=622.3$ .

Example 849: *N*2-(4-{4-amino-1-[1-(4-pyridylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

Yield 57 mg, 18%.

- $^1H$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$  1.91 (m, 2H), 2.28 (m, 4H), 3.95 (m, 2H), 3.59 (s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.71 (m, 1H), 7.17 (m, 1H), 7.34 (m, 6H), 7.59 (d,  $J=8.03$  Hz, 1H), 7.71 (d,  $J=7.94$  Hz, 1H), 8.11 (d,  $J=8.14$  Hz, 1H), 8.25 (s, 1H), 8.52 (d,  $J=5.78$  Hz, 2H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-  
25 Column: Genesis, C18, 3  $\mu$ m, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.):  $R_T=2.50$  min.  $MH^+=588.3$ .

Example 850: N2-(4-{4-amino-1-[3-(4-methylpiperazino)propyl]-1H-pyrazolo[3,4-  
d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-  
indolecarboxamide

A. 1-(3-bromopropyl)-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine

- 5 A suspension of 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (10.00 g, 38.31 mmol) in tetrahydrofuran (150 mL) was treated with 3-bromo-1-propanol (15.98 g, 114.93 mmol) and triphenylphosphine (20.1 g, 76.62 mmol). Diethylazodicarboxyate (13.34 g, 76.62 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at 0°C for 30 min, after which the ice bath
- 10 was removed and was stirred for 30 minutes at room temperature. The reaction mixture was partially concentrated and ethyl acetate (200 mL) was added. The precipitate was filtered and the filtrate was concentrated to dryness. The crude compound was purified by flash chromatography on silica gel using 100% ethyl acetate as the eluent. The afforded 7.8 g (53%) of 1-(3-bromopropyl)-3-iodo-1H-
- 15 pyrazolo[3,4-*d*]pyrimidin-4-amine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.230 (s, 1H), 4.419-4.385 (t, 2H), 3.530-3.498 (t, 2H), 2.370-2.304 (q, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R<sub>t</sub> 2.05 min (100%), MH<sup>+</sup> 422.9.

20

B. 3-iodo-1-[3-(4-methylpiperazino)propyl]-1H-pyrazolo[3,4-  
*d*]pyrimidin-4-amine

- A suspension of 1-(3-bromopropyl)-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.31 mmol) in dimethylformamide (10 mL) was treated with 1-methylpiperazine (0.157 g, 1.572 mmol) and triethylamine (0.133 g, 1.31 mmol).
- 25 The reaction mixture was stirred at 70°C for 66.25 h. Solvent was removed under reduced pressure. Dichloromethane (15 mL) and 1 N hydrochloric acid (20 mL) were added. The layers were partitioned and the aqueous layer was washed with dichloromethane (100 mL). The aqueous layer was neutralized to pH 13 and then
- 30 extracted with dichloromethane (250 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient; 20% methanol in dichloromethane to 50% methanol in dichloromethane

- over 55 minutes on a 35 g ISCO column. The column afforded 0.238 g (45%) of pure 3-iodo-1-[3-(4-methylpiperazino)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.191 (s, 1H), 4.308-4.273 (t, 2H), 2.262-2.228 (m, 10H), 1.944-1.877(m, 2H); LCMS (Thermoquest AQA single-quad MS, 5 Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R<sub>t</sub> 0.75 min (100%), MH<sup>+</sup> 402.1.

- C. *N*2-(4-{4-amino-1-[3-(4-methylpiperazino)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A solution of 3-iodo-1-[3-(4-methylpiperazino)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.188 g, 0.469 mmol) in ethylene glycol dimethyl ether (16 mL) was treated with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.209 g, 0.516 mmol), tetrakis(triphenylphosphine)palladium (0.033 g, 0.028 mmol), and a solution of sodium carbonate (0.119 g, 1.13 mmol) in water (8 mL). The reaction mixture was stirred for 4.5 h at 80°C. The organic solvent was removed under reduced pressure and ethyl acetate (200 mL) was added. The layers were partitioned and the aqueous layer was extracted with ethyl acetate (400 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient of 20% methanol in dichloromethane to 50% methanol in dichloromethane. The column afforded 0.078 g (30%) of pure *N*2-(4-{4-amino-1-[3-(4-methylpiperazino)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.442 (s, 1H), 8.258 (s, 1H), 8.122-8.1076 (d, 1H, *J* = 8.16 Hz), 7.719-7.6991 (d, 1H, *J* = 7.96 Hz), 7.6005-7.5793 (d, 1H, *J* = 8.48 Hz), 7.349-7.294 (m, 4H), 7.172-7.135 (t, 1H), 4.405-4.371 (m, 2H), 4.04 (s, 3H), 3.958 (s, 3H), 3.291 (m, 2H), 2.5 (m, 3H), 2.45-2.337 (m, 5H), 2.30-2.10 (m, 3H), 2.022-2.005 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R<sub>t</sub> 2.05 min (100%), MH<sup>+</sup> 554.3.

Example 851: *N*2-[4-[4-amino-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

30

- A. 3-iodo-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 1-(3-bromopropyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-

amine (0.500 g, 1.31 mmol) in dimethylformamide (10 mL) was treated with morpholine (0.137 g, 1.572 mmol) and triethylamine (0.133 g, 1.31 mmol). The reaction mixture was stirred at 70°C for 66.25 h. Solvent was removed under reduced pressure. Dichloromethane (15 mL) and 1 N hydrochloric acid (20 mL) were added. The layers were partitioned and the aqueous layer was washed with dichloromethane (100 mL). The aqueous layer was neutralized to pH 14 and then extracted with dichloromethane (250 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient of 10% methanol in dichloromethane to 50% methanol in dichloromethane over 58 minutes on a 35 g ISCO column. The column afforded 0.244 g (48%) of pure 3-iodo-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.194 (s, 1H), 4.327-4.293 (t, 2H), 3.485-3.364 (m, 4H), 2.253-2.238 (m, 6H), 1.963-1.895(m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R<sub>t</sub> 0.71 min (100%), MH<sup>+</sup> 389.0.

B. N2-{4-[4-amino-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A solution of 3-iodo-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.244 g, 0.629 mmol) in ethylene glycol dimethyl ether (16 mL) was treated with N2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.281 g, 0.692 mmol), tetrakis(triphenylphosphine)palladium (0.044 g, 0.038 mmol), and a solution of sodium carbonate (0.160 g, 1.51 mmol) in water (8 mL). The reaction mixture was stirred for 4.5 h at 80°C. The organic solvent was removed under reduced pressure and ethyl acetate (200 mL) was added. The layers were partitioned and the aqueous layer was extracted with ethyl acetate (400 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient of 10% methanol in dichloromethane to 50% methanol in dichloromethane

as the eluent. The column afforded 0.191 g (56%) of pure *N*2-{4-[4-amino-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.440 (s, 1H), 8.260 (s, 1H), 8.1229-8.1026 (d, 1H, *J* = 8.12 Hz), 7.7184-7.6986 (d, 1H, *J* = 7.92 Hz), 7.5983-7.578 (d, 1H, *J* = 8.08 Hz), 7.345-7.290 (m, 4H), 7.172-7.133 (m, 1H), 4.421-4.386 (m, 2H), 4.04 (s, 3H), 3.958 (s, 3H), 3.521-3.500 (m, 4H), 2.349-2.314 (m, 6H), 2.035-2.001 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) *R*<sub>t</sub> 2.05 min (100%), MH<sup>+</sup> 541.3.

Example 852: *N*2-(4-{4-amino-1-[3-(1*H*-1-imidazolyl)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A. 1-[3-(1*H*-1-imidazolyl)propyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 1-(3-bromopropyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.31 mmol) in dimethylformamide (10 mL) was treated with imidazole (0.107 g, 1.572 mmol) and triethylamine (0.133 g, 1.31 mmol). The reaction mixture was stirred at 70°C for 25.5 h. Solvent was removed under reduced pressure. Dichloromethane (15 mL) and 1 N hydrochloric acid (20 mL) were added. The layers were partitioned and the aqueous layer was washed with dichloromethane (100 mL). The aqueous layer was neutralized to pH 14 and then extracted with dichloromethane (250 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane as the eluent. The column afforded 0.086 g (18%) of pure 1-[3-(1*H*-1-imidazolyl)propyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.211 (s, 1H), 7.896 (s, 1H), 7.264 (s, 1H), 6.96 (s, 1H), 4.32-4.227 (m, 2H), 4.011-3.977 (m, 2H), 2.329-2.215 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min,

0.8 to 0.5 mL/min) R<sub>t</sub> 0.46 min (100%), MH<sup>+</sup> 370.0.

B. *N*2-[4-{4-amino-1-[3-(1*H*-1-imidazolyl)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

- 5 A suspension of 1-[3-(1*H*-1-imidazolyl)propyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.086 g, 0.233 mmol) in ethylene glycol dimethyl ether (4 mL) was treated with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.104 g, 0.256 mmol),
- 10 tetrakis(triphenylphosphine)palladium (0.016 g, 0.014 mmol), and a solution of sodium carbonate (0.059 g, 0.56 mmol) in water (2 mL). The reaction mixture was stirred for 24 h at 80°C. The organic solvent was removed under reduced pressure and dichloromethane (25 mL) was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic
- 15 layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient of 5% methanol in dichloromethane to 50% methanol in dichloromethane on a 10 g ISCO column. The column afforded 0.06 g (49%) of pure *N*2-[4-{4-amino-1-[3-(1*H*-1-imidazolyl)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-
- 20 3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.443 (s, 1H), 8.278 (s, 1H), 8.1324-8.1121 (d, 1H, *J* = 8.12 Hz), 7.744-7.699 (m, 2H), 7.6-7.579 (d, 1H, *J* = 8.4 Hz), 7.365-7.283 (m, 5H), 7.172-7.135 (m, 1H), 6.939 (s, 1H), 4.36-4.326 (m, 2H), 4.079-4.019 (m, 5H), 3.964 (s, 3H), 2.324-2.309 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column,
- 25 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R<sub>t</sub> 2.25 min (100%), MH<sup>+</sup> 522.3.

Example 853: *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

- 30 A. *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate

A suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.0 g, 19.15



mmol) in tetrahydrofuran (100 mL) was treated with tert-butyl 3-hydroxy-1-pyrrolidinecarboxylate (5.38 g, 28.73 mmol) and triphenylphosphine (7.53 g, 28.73 mmol). The reaction mixture was cooled to 0°C on an ice bath.

Diethylazodicarboxylate (5.0 g, 28.73 mmol) was slowly added to the reaction mixture. The solvent was removed under reduced pressure after 6 days. The crude oil was used directly in the subsequent reaction without further analysis.

B. 3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride

A suspension of the crude tert-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate in acetone (100 mL) was treated with 6 N hydrochloric acid (50 mL). The reaction mixture was stirred at 40°C for 15 hours. The initial precipitate was filtered and confirmed by LCMS to be impurities. The reaction mixture was allowed to sit at room temperature and a precipitate formed over night. The precipitate was filtered and washed with diethyl ether. The filtration afforded 2.186 g (31%) of pure 3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.8815 (s, 1H), 8.9923 (br.s, 1H), 8.4803 (s, 1H), 7.82 (br.s, 1H), 5.5908-5.5295 (m, 1H), 3.7131-3.6706 (m, 1H), 3.5590-3.5003 (m, 1H), 3.4466-3.4174 (m, 2H), 2.4592-2.4255 (m, 1H), 2.4064-2.3146 (m, 1H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3µm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R<sub>t</sub> 1.09 min (100%), MH<sup>+</sup> 331.0.

C. N2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A suspension of 3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (2.186 g, 5.96 mmol) in ethylene glycol dimethyl ether (50 mL) was treated with N2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (2.66 g, 6.56 mmol), tetrakis(triphenylphosphine)palladium (0.413g, 0.358 mmol), and a solution of sodium carbonate (2.65 g, 25.03 mmol) in water (25 mL). The reaction mixture

was stirred for 24 h at 80°C. The organic solvent was removed under reduced pressure. Dichloromethane (100 mL) and 1N sodium hydroxide (50 mL) were added. The product precipitated out of the aqueous layer. The aqueous layer was evaporated under reduced pressure. The resulting solid was washed with copious amounts of dichloromethane and ethyl acetate. The organic solvent was removed under reduced pressure to give 2.218 g (77%) of pure *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.443 (s, 1H), 8.256 (s, 1H), 8.1168-8.0965 (d, 1H, *J* = 8.12 Hz), 7.7181-7.6983 (d, 1H, *J* = 7.92 Hz), 7.598-7.5778 (d, 1H, *J* = 8.08 Hz), 7.349-7.291 (m, 4H), 7.171-7.132 (m, 1H), 5.332-5.313 (m, 1H), 4.041 (s, 3H), 3.96 (s, 3H), 3.224-3.058 (m, 3H), 2.926-2.910 (m, 1H), 2.213-2.158 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) *R*<sub>t</sub> 2.09 min (100%), MH<sup>+</sup> 483.3.

15

Example 854: *N*2-[4-(4-amino-1-{1-[(1-methyl-1*H*-2-imidazolyl)methyl]tetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.250 g, 0.518 mmol) in dichloroethane (5 mL) was treated with 1-methyl-2-imidazolecarboxaldehyde (0.115 g, 1.04 mmol) and sodium triacetoxy borohydride (0.220 g, 1.04 mmol). The reaction mixture was stirred at room temperature for 18 h under a nitrogen atmosphere. Sodium hydroxide (1N, 15 mL) was added to the reaction mixture and was stirred for 1h. The organic layer was removed under reduced pressure and dichloromethane was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (15 min), 15% methanol in dichloromethane (15 min), 20% methanol in dichloromethane (20 min) and 50% methanol in dichloromethane (5 min) as the eluent. The column

30

afforded 0.060 g (20%) of pure *N*2-[4-(4-amino-1-{1-[(1-methyl-1*H*-2-imidazolyl)methyl]tetrahydro-1*H*-3-pyrrolyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.446 (s, 1H), 8.249 (s, 1H), 8.1312-8.1108 (d, 1H, *J* = 8.16 Hz), 7.7207-7.7008 (d, 1H, *J* = 7.96 Hz), 7.6023-7.5812 (d, 1H, *J* = 8.44 Hz), 7.356-7.293 (m, 4H), 7.174-7.120 (m, 2H), 6.822 (s, 1H), 5.425-5.391 (m, 1H), 4.044 (s, 3H), 3.962 (s, 3H), 3.693 (m, 2H), 3.651 (s, 3H), 2.86-2.797 (m, 3H), 2.368-2.323 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) *R*<sub>t</sub> 2.34 min (100%), *MH*<sup>+</sup> 577.3.

Example 855: *N*2-[4-[4-amino-1-(1-isopropyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.250 g, 0.518 mmol) in dichloroethane (5 mL) was treated with acetone (1.96 g, 33.15 mmol) and sodium triacetoxo borohydride (0.220 g, 1.04 mmol). The reaction mixture was stirred at room temperature for 18 h under a nitrogen atmosphere. Sodium hydroxide (1*N*, 15 mL) was added to the reaction mixture and was stirred for 1h. The organic layer was removed under reduced pressure and dichloromethane was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (15 min), 15% methanol in dichloromethane (15 min), 20% methanol in dichloromethane (20 min) and 50% methanol in dichloromethane (5 min) as the eluent. The column afforded 0.123 g (44%) of pure *N*2-[4-[4-amino-1-(1-isopropyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.449 (s, 1H), 8.265 (s, 1H), 8.127-8.1068 (d, 1H, *J* = 8.08 Hz), 7.7196-7.6999 (d, 1H, *J* = 7.88 Hz), 7.6013-7.5803 (d, 1H, *J* = 8.4 Hz), 7.351-7.299 (m, 4H), 7.173-7.135 (m, 1H), 5.394 (m,

1H), 4.042 (s, 3H), 3.961 (s, 3H), 2.793 (m, 3H), 2.337 (m, 3H), 1.068 (br.s, 6H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3 $\mu$ m particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R<sub>t</sub> 2.38 min (100%), MH<sup>+</sup> 525.3.

5

Example 856: *N*2-[4-(4-amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl)-1*H*-

- 10 pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.250 g, 0.518 mmol) in dimethylformamide (5 mL) was treated with 2-bromoethyl methyl ether (0.079 g, 0.569 mmol) and potassium carbonate (0.143 g, 1.04 mmol). The reaction mixture was stirred at 65°C for 18 h under a nitrogen atmosphere. Water (25 mL) was added to the reaction mixture. The
- 15 precipitate formed was filtered and dried on the lyophilizer. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (15 min), 15% methanol in dichloromethane (15 min), 20% methanol in dichloromethane (20 min) and 50% methanol in dichloromethane (5 min) as the eluent. The column afforded 0.082 g (29%) of pure *N*2-[4-(4-amino-1-
- 20 [1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  9.447 (s, 1H), 8.265 (s, 1H), 8.1278-8.1075 (d, 1H, *J* = 8.12 Hz), 7.7192-7.6993 (d, 1H, *J* = 7.96 Hz), 7.5996-7.5799 (d, 1H, *J* = 7.88 Hz), 7.349-7.295 (m, 4H), 7.172-7.133 (m, 1H), 5.42 (m, 1H), 4.042 (s, 3H), 3.96 (s, 3H), 3.479 (m, 2H),
- 25 3.266-3.258 (m, 3H), 2.95-2.60 (m, 4H), 2.332 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3 $\mu$ m particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R<sub>t</sub> 2.34 min (100%), MH<sup>+</sup> 541.3.

- 30 Example 857: *N*2-[4-(4-amino-1-[1-(1*H*-4-imidazolylmethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl)-1*H*-

- pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.200 g, 0.415 mmol) in dichloroethane (5 mL) was treated with 4-formylimidazole (0.08 g, 0.83 mmol) and sodium triacetoxy borohydride (0.176 g, 0.83 mmol). The reaction mixture was stirred at room temperature for 24 h under a nitrogen atmosphere. Sodium hydroxide (1*N*, 15 mL) was added to the reaction mixture and was stirred for 1h. The organic layer was removed under reduced pressure and dichloromethane was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (20 min), 15% methanol in dichloromethane (10 min), 20% methanol in dichloromethane (10 min) and 50% methanol in dichloromethane (8 min) as the eluent. The column afforded 0.074 g (25%) of pure *N*2-[4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.446 (s, 1H), 8.252 (s, 1H), 8.126-8.1082 (d, 1H, *J* = 8.16 Hz), 7.7198-7.7 (d, 1H, *J* = 7.92 Hz), 7.6-7.569 (m, 2H), 7.35-7.298 (m, 4H), 7.171-7.134 (m, 1H), 6.946 (s, 1H), 5.422-5.385 (m, 1H), 4.043 (s, 3H), 3.961 (s, 3H), 3.691 (s, 2H), 3.175-3.162 (m, 2H), 2.9-2.883 (m, 3H), 2.385-2.332 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) *R*<sub>t</sub> 2.13 min (100%), MH<sup>+</sup> 563.3.

- Example 858: *N*2-[4-(4-amino-1-{1-[(3-methyl-1*H*-4-pyrazolyl)methyl]tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

- A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.200 g, 0.415 mmol) in dichloroethane (5 mL) was treated with 3-methyl-1*H*-pyrazol-4-carboxaldehyde (0.091 g, 0.83 mmol) and sodium triacetoxy borohydride (0.176 g, 0.83 mmol). The reaction mixture was stirred at room temperature for 24 h under a nitrogen atmosphere. Sodium hydroxide (1*N*, 15 mL)

was added to the reaction mixture and was stirred for 1h. The organic layer was removed under reduced pressure and dichloromethane was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (100 mL) and ethyl acetate (100 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (15 min), 15% methanol in dichloromethane (10 min), 20% methanol in dichloromethane (10 min) and 50% methanol in dichloromethane (8 min) as the eluent. The column afforded 0.106 g (44%) of pure *N*2-[4-(4-amino-1-{1-[(3-methyl-1*H*-4-pyrazolyl)methyl]tetrahydro-1*H*-3-pyrrolyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.446 (s, 1H), 8.247 (s, 1H), 8.1275-8.1071 (d, 1H, *J* = 8.16 Hz), 7.72-7.7003 (d, 1H, *J* = 7.96 Hz), 7.6004-7.5793 (d, 1H, *J* = 8.44 Hz), 7.398-7.286 (m, 5H), 7.172-7.134 (m, 1H), 5.379 (m, 1H), 4.0443 (s, 3H), 3.962 (s, 3H), 3.492 (m, 2H), 3.1 (m, 1H), 2.75 (m, 3H), 2.352-2.335 (m, 2H), 1.909 (s, 3H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) *R*<sub>t</sub> 2.17 min (100%), MH<sup>+</sup> 577.3.

20 Example 859: *N*2-(4-{4-amino-1-[(3*R*)-1-methyltetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

*N*2-(4-{4-amino-1-[(3*R*)-1-methyltetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from (5*S*)-(-)-3-pyrrolidinol in a manner analogous to that used for the preparation of *rac*-*N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine. The compound was formed as a white solid (0.195 g, 53%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 2.31-2.35 (m, 2 H), 2.32 (s, 3 H), 2.35 (s, 3 H), 2.40 (s, 3 H), 2.70-2.77 (m, 3 H), 3.05 (t, 1 H), 5.40 (m, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.85 (s, 1 H); RP-HPLC *R*<sub>t</sub> 11.090 min, 99% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate,

buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column); *m/z* 455 (*MHT*<sup>+</sup>).

Example 860: *N*2-(4-{4-amino-1-[(3*S*)-1-methyltetrahydro-1*H*-3-pyrrolyl]-1*H*-

5                      pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

*N*2-(4-{4-amino-1-[(3*S*)-1-methyltetrahydro-1*H*-3-pyrrolyl]-1*H*-  
pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was  
prepared from (*R*)-(-)-3-pyrrolidinol in a manner analogous to that used for the  
10       preparation of *rac-N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-  
pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine. The  
compound was formed as a white solid (0.126 g, 20%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400  
MHz) <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 2.31-2.35 (m, 2 H), 2.31 (s, 3 H), 2.35 (s, 3  
H), 2.40 (s, 3 H), 2.67-2.76 (m, 3 H), 3.05 (t, 1 H), 5.40 (m, 1 H), 6.80 (s, 1 H), 7.11  
15       (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.84 (s, 1 H); RP-HPLC Rt  
11.129 min, 100% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate,  
buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  
 $\mu$ m, 150 x 3.9 mm column); *m/z* 455 (*MHT*<sup>+</sup>).

20       Example 861: *rac-N*2-(4-{4-amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-  
pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-isopropyl-5-  
methyl-1,3-benzoxazol-2-amine

*rac-N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-  
pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-isopropyl-1,3-benzoxazol-2-amine was  
25       prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-  
pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.515 mmol) and *N*2-[4-(4,4,5,5-  
tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-7-isopropyl-1,3-benzoxazol-2-amine  
(0.244 g, 0.644 mmol) in a manner similar to that used for the preparation of *cis-N*2-  
(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-  
30       yl)-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-  
white solid (0.067 g, 25%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) 1.361 (d, 6 H), 2.30 (m,  
2 H), 2.66 (m, 2 H), 2.76-2.83 (m, 3 H), 3.17 (t, 1 H), 3.24 (s, 3 H), 3.38 (m, 1 H),  
3.45 (t, 2 H), 5.37 (m, 1 H), 7.04 (d, 1 H), 7.18 (t, 1 H), 7.32 (d, 2 H), 7.67 (d, 2 H),

7.95 (d, 2 H), 8.24 (s, 1 H), 10.88 (s, 1 H); RP-HPLC Rt 12.337 min, 94% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min;  $\lambda$  = 254 nm; Deltapak C18, 300 Å, 5  $\mu$ m, 150 x 3.9 mm column);  $m/z$  513 ( $MH^+$ ).

5

Example 861: *cis*-Ethyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate

3-Iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.52 g, 2.0 mmol), ethyl 4-hydroxycyclohexanecarboxylate (0.806 mL, 5.0 mmol, triphenylphosphine (1.05 g, 4.0 mmol), diethyl azodicarboxylate (0.628 mL, 4.0 mmol) were suspended in tetrahydrofuran (15 mL), and the mixture was stirred at ambient temperature under a gentle flow of nitrogen for 48 h. The mixture was diluted with water (50 mL), and extracted with ethyl acetate (3 x 50 mL). The organic fractions were combined, dried over magnesium sulfate, filtered, and concentrated. The residue was partially purified by flash column chromatography (100% ethyl acetate) to afford ethyl 4-(4-amino-5-iodo-7*H*-pyrrolo[3,4-*d*]pyrimidin-7-yl)-1-cyclohexanecarboxylate as a mixture of *cis*- and *trans*-diastereomers, along with triphenylphosphine oxide. Repurification of the mixture by flash column chromatography on silica gel deactivated with triethylamine (0.5 % methanol/dichloromethane as eluant) afforded the desired *cis*-ethyl 4-(4-amino-5-iodo-7*H*-pyrrolo[3,4-*d*]pyrimidin-7-yl)-1-cyclohexanecarboxylate as a yellow solid (0.260 g, 0.625 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  9.55 min; MS ( $MH^+$ )<sup>+</sup> 416.

*cis*-Ethyl 4-(4-amino-5-iodo-7*H*-pyrrolo[3,4-*d*]pyrimidin-7-yl)-1-cyclohexanecarboxylate (0.10 g, 0.24 mmol) was combined with *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.088 g, 0.24 mmol), sodium carbonate (0.064 g, 0.60 mmol), tetrakis(triphenylphosphine)-palladium (0) (0.014 g, 0.012 mmol), ethylene glycol dimethyl ether (2 mL) and water (1 mL), and the mixture was heated at 85 °C in a resealable Schlenk tube for 14 h. The reaction mixture was cooled to ambient temperature, diluted with water (10 mL), and extracted with 10% methanol dichloromethane (3 x 20 mL). The organic fractions were combined, dried over

30



magnesium sulfate, filtered, and concentrated. Purification of the product by flash column chromatography on silica gel deactivated with triethylamine (2.5% methanol/dichloromethane as eluant) afforded *cis*-ethyl 4-(4-amino-3-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate as a white solid (0.040 g, 0.076 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  12.63 min;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.85 (s, 1H), 8.23 (s, 1H), 7.92 (d, 2H), 7.64 (d, 2H), 7.11 (s, 1H), 6.80 (s, 1H), 4.66 (m, 1H), 4.10 (qt, 2H), 3.27 (m, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.08 (m, 6H), 1.61 (m, 2H), 1.20 (t, 3H).

Example 862: *cis*-Methyl 4-(4-amino-3-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate

*cis*-Ethyl 4-(4-amino-3-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate (0.030 g, 0.057 mmol), sodium methoxide (0.0033 g, 0.063 mmol) and methanol (2 mL) were combined and heated in a resealable Schlenk tube for 48 h at 75  $^{\circ}\text{C}$ . Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column,  $R_t$  15.6-16.5 min) afforded *cis*-methyl 4-(4-amino-3-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate as a white powder (0.010 g, 0.020 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  11.82 min;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.85 (s, 1H), 8.23 (s, 1H), 7.92 (d, 2H), 7.65 (d, 2H), 7.12 (s, 1H), 6.80 (s, 1H), 4.67 (m, 1H), 3.63 (s, 3H), 3.27 (m, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.07 (m, 6H), 1.61 (m, 2H).

Example 863: *cis*-4-(4-Amino-3-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylic acid

*cis*-Ethyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate (0.10 g, 0.19 mmol), aqueous sodium hydroxide (1 M, 2 mL, 2 mmol), and methanol (2 mL) were combined and heated under an air condenser at 70 °C for 14 h. The residue was acidified with aqueous hydrochloric acid (3 M, 2 mL, 6 mmol), and extracted with 10% methanol/dichloromethane (3 x 20 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column,  $R_t$  8.8-10.9 min) afforded *cis*-4-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylic acid as a cream-colored powder (0.026 g, 0.052 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  9.03 min; MS (MH)<sup>+</sup> 498.

Example 864: *cis*-1-[4-(4-Methylpiperazino)cyclohexyl]-3-[4-(2-pyrimidinylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine 4-Bromoaniline (0.300 g, 1.74 mmol) and 2-chloropyrimidine (0.200 g, 1.74 mmol) were heated neat at 150 °C in a 25 mL flask for 2 h. The reaction mixture was cooled to ambient temperature, and purification of the residue by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column,  $R_t$  13.8-15.9 min) afforded *N*-(4-bromophenyl)-*N*-(2-pyrimidinyl)amine as a yellow solid (0.135 g, 0.54 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  11.08 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  9.78 (s, 1H), 8.50 (d, 2H), 7.76 (d, 2H), 7.45 (d, 2H), 6.87 (t, 1H).

*N*-(4-Bromophenyl)-*N*-(2-pyrimidinyl)amine was converted to the title compound using a procedure similar to the one described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine. Purification of the product

by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8  $\mu$  Hypersil HS C18, 250 x 21 mm column,  $R_t$  4.0-5.0 min) afforded *cis*-1-[4-(4-methylpiperazino)cyclohexyl]-3-[4-(2-pyrimidinylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a white powder (0.095 g, 0.196 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5  $\mu$  Hypersil HS C18, 250 x 4.6 mm column)  $R_t$  5.38 min; MS (MH)<sup>+</sup> 485.

Example 865: *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1*H*-2-indolecarboxamide acetate

A. 1-(2-chloro-4-pyridyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4.12 g, 0.016 mol) in *N,N*-dimethylformamide (50 mL) was reacted with 60% sodium hydride in oil (0.75 g, 0.019 mol) at ambient temperature. The mixture was stirred for 15 minutes, and 2-chloro-4-nitropyridine (3.00 g, 0.019 mol) was added. The mixture was heated at 100° C for 18 hours. The mixture was cooled to room temperature and the precipitate was filtered, washing with *N,N*-dimethylformamide (20 mL), and then slurried in ethyl acetate (50 mL) for four hours. The solid was filtered and dried *in vacuo* to give 1-(2-chloro-4-pyridyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.39 g, 0.009 mol) as a tan solid:

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  8.52 (d, 1H), 8.43 (s, 1H), 8.40 (d, 1H), 8.25 (dd, 1H); RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 10 min, 1mL/min)  $R_t$  10.29 min.;

MS: MH<sup>+</sup> 373.

B. *N*2-[4-[4-amino-1-(2-chloro-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A suspension of 1-(2-chloro-4-pyridyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.95 g, 0.00256 mol) in dimethoxyethane (30 mL) and water (60 mL) was reacted with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (1.14 g, 0.00281 mol), sodium carbonate (0.68 g,

0.00640 mol) and tetrakis (triphenylphosphine) palladium (0) (0.30 g, 0.00026 mol) at 80° C for 3 days. The solid was filtered and washed with water. The solid was triturated with ethyl acetate (75 mL) for 6 hours and filtered, washing with ethyl acetate (20 mL). The solid was then triturated with methanol (75 mL) for 6 hours and filtered, washing with methanol (20 mL). The solid was dried *in vacuo* to give crude *N*2-{4-[4-amino-1-(2-chloro-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.672 g, 0.00128 mol) as a tan solid:

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.48 (s, 1H), 8.55-8.58 (m, 2H), 8.50 (s, 1H), 8.44 (dd, 1H), 8.21 (d, 1H), 7.72 (d, 1H), 7.60 (d, 1H), 7.49 (d, 1H), 7.43 (dd, 1H), 7.31-7.38 (m, 2H), 7.16 (t, 1H), 4.05 (s, 3H), 4.00 (s, 1H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile ~ 0.1M ammonium acetate over 10 min, isocratic at 95% for 3 min., 1mL/min) R<sub>t</sub> 12.70 min.; MS: MH<sup>+</sup> 525.

C. *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1*H*-2-indolecarboxamide acetate

A suspension of *N*2-{4-[4-amino-1-(2-chloro-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.120 g, 0.00023 mol) in 1-methylpiperazine (5 mL) heated at 120° C for 5 days. The solvent was removed *in vacuo* and the residue was slurried in diethyl ether (25 mL) for 4 hours. The mixture was filtered, washing with diethyl ether (105 mL) and dried *in vacuo*. The crude material was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 A, 25 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 mL/min). The acetonitrile was removed in *vacuo* and the aqueous mixture was lyophilized to give *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-1*H*-2-indolecarboxamide acetate (0.030 g, 0.00005 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.47 (s, 1H), 8.44 (s, 1H), 8.12 (d, 1H), 7.77 (s, 1H), 7.72 (d, 1H), 7.68 (d, 1H), 7.60 (d, 1H), 7.30-7.37 (m, 3H), 7.26 (d, 1H), 7.15 (t, 1H), 4.06 (s, 3H), 3.50-3.58 (m, 4H), 2.38-2.46 (m, 4H), 2.24 (s, 3H), 1.91 (s, 3H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)  $R_t$  15.33 min.;  
MS:  $MH^+$  575.

- 5 Example 866: *N*2-{4-[4-amino-1-(2-morpholino-4-pyridyl)-1*H*-pyrazolo[3,4-  
*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-  
indolecarboxamide

- A suspension of *N*2-{4-[4-amino-1-(2-chloro-4-pyridyl)-1*H*-pyrazolo[3,4-  
*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.120 g,  
10 0.00023 mol) and morpholine (10 mL) was heated at 100° C for 6 days. The solvent  
was removed *in vacuo* and the residue was slurried in water (25 mL) for 4 hours.  
The mixture was filtered and the crude solid was purified by preparative RP-HPLC  
(Rainin C18, 8mm, 300 A, 25 cm; 35%-80% acetonitrile - 0.050 M ammonium  
acetate over 20 min, 21 ml/min). The acetonitrile was removed in *vacuo* and the  
15 aqueous mixture was lyophilized to give *N*2-{4-[4-amino-1-(2-morpholino-4-  
pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-  
indolecarboxamide (0.048 g, 0.00008 mol) as a white solid.  
 $^1H$  NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.48 (s, 1H), 8.44 (s, 1H), 8.27 (d, 1H), 8.18 (d, 1H),  
7.82 (d, 1H), 7.74 (dd, 1H), 7.72 (d, 1H), 7.60 (d, 1H), 7.46 (d, 1H), 7.41 (dd, 1H), 7.36  
20 (s, 1H), 7.34 (t, 1H), 7.16 (t, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 3.72-3.78 (m, 4H), 3.49-  
3.56 (m, 4H);

RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M  
ammonium acetate over 20 min, 1mL/min)  $R_t$  17.89 min.;  
MS:  $MH^+$  576.

25

Example 867: (*S*)-*N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-  
pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-  
amine

A. (*R*)-*tert*-butyl 3-hydroxy-1-piperidinecarboxylate

- 30 A mixture of (*R*)-3-hydroxy piperidine hydrochloride (10 g, 0.073 mol), di-  
*tert*-butyl dicarbonate (20 g, 0.091 mol) and sodium carbonate (19 g, 0.182 mol) in  
dioxane (80 mL) and water (80 mL) was stirred at room temperature under an

atmosphere of nitrogen for 18 hours. The organic solvent was removed under the reduced pressure. The aqueous layer was extracted with diethyl ether (2 x 200 mL). The organic layer was washed with brine and dried over magnesium sulfate. The solvent was removed under the reduced pressure to yield clear oil of (*R*)-*tert*-butyl 3-hydroxy-1-piperidinecarboxylate (17.6 g, 0.087 mol). The crude product was carried to the next reaction.

<sup>1</sup>H NMR (Chloroform-*d*, 400 MHz)  $\delta$  3.76 (m, 1H), 3.67 (br, 1H), 3.55 (br, 1H), 2.92 (m, 2H), 2.75 (s, 1H), 1.85 (br, 1H), 1.72 (br, 1H), 1.46 (br, 11H)

GC-MS: MH<sup>+</sup> 202

10

B. (*S*)-*Tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate

To a mixture of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2 g, 0.0077 mol), (*R*)-*tert*-butyl 3-hydroxy-1-piperidinecarboxylate (2.3 g, 0.012 mol), and triphenylphosphine (3 g, 0.012 mol) in tetrahydrofuran (70 mL), diethyl azodicarboxylate (2 g, 0.012 mol) was added at 0 °C. The mixture was stirred at room temperature under an atmosphere of nitrogen for 2 days. In order to complete the reaction, additional (*R*)-*tert*-butyl 3-hydroxy-1-piperidinecarboxylate (0.62 g, 0.003 mol), and triphenylphosphine (0.81 g, 0.012 mol), and diethyl azodicarboxylate (0.6 g, 0.003 mol) were added to the mixture. The mixture was stirred at room temperature under an atmosphere of nitrogen for additional 18 hours. The solvent was removed under the reduced pressure to yield crude (*S*)-*tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate, which was used crude for the next reaction.

25 RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.0 min.

MS: MH<sup>+</sup> 445

30 C. (*S*)-3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

To a mixture of (*S*)-*tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (3.4 g, 0.0077 mol) in acetone (80mL)

- was added an aqueous 6N solution of hydrogen chloride (20 mL) at room temperature. The mixture was stirred at 45 °C for 4 hours, then at room temperature for 18 hours. Acetone was removed under reduced pressure, and the aqueous layer was washed with toluene (2 x 20 mL) and dichloromethane (2 x 20 mL). The aqueous layer was basified with an aqueous 5N solution of sodium hydroxide (25 mL) at 0 °C. The aqueous layers were concentrated to dryness, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8 $\mu$ m, 250 x 21.1 mm; 2% - 30% over 15 min with 0.1 M ammonium acetate, 21mL/min) to yield (*S*)-3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.75 g, 0.0019 mol).
- 10 RP-HPLC (Hypersil C18, 5 $\mu$ m, 250 x 4.6 mm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.2 min.
- MS: MH<sup>+</sup> 345

D. (*S*)-3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

- To a mixture of (*S*)-3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.75 g, 0.0019 mol) and potassium carbonate (0.77 g, 0.00568mol) in *N,N*-dimethylformamide (30 mL) were added 2-bromoethyl methyl ether (0.27 g, 0.0019 mol) and potassium iodide (0.0016 g, 0.000095 mol) at room temperature.
- 20 The mixture was stirred at 65 °C under an atmosphere of nitrogen for 16 hours. The reaction mixture was cooled to room temperature, and 2-bromoethyl methyl ether (0.27 g, 0.0019 mol) and potassium iodide (0.0016 g, 0.000095 mol) were added. The mixture was stirred at 65 °C under an atmosphere of nitrogen for 4 hours. The solvent was removed under the reduced pressure. The residue was partitioned
- 25 between saturated sodium bicarbonate solution (25 mL) and dichloromethane (50 mL). The aqueous layer was extracted with dichloromethane (4 x 50 mL). The solvents were evaporated under the reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8 $\mu$ m, 250 x 21.1 mm; 2% - 30% over 15 min with 0.1 M ammonium acetate, 21mL/min) to (*S*)-3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.64 g, 0.0014 mol).
- 30 RP-HPLC (Hypersil C18, 5 $\mu$ m, 250 x 4.6 mm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.9 min.

MS: MH<sup>+</sup> 403

E. (S)-N2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A mixture of (S)-3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine acetate (0.64 g, 0.0014 mol), N-(5,7-dimethyl-1,3-benzoxazol-2-yl)-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.64 g, 0.00175 mol, 1.2 eq.),

tetrakis(triphenylphosphine)palladium (0.081 g, 0.00007 mol) and sodium carbonate (0.37 g, 0.0035 mol) in N,N-dimethylformamide (15 mL) and water (7 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water (25 mL) and dichloromethane (50 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish oil, which was purified by flash column chromatography on silica using 2 % - 10 % methanol / dichloromethane as a mobile phase to give (S)-N2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.60 g, 0.0012mol).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.85 (s, 1H), 8.25 (s, 1H), 7.93 (d, 2H), 7.65 (d, 2H), 7.11 (s, 1H), 6.80 (s, 1H), 4.77 (br, 1H), 3.36 (m, 2H), 3.25 (s, 3H), 3.04 (br, 1H), 2.90 (br, 1H), 2.55 (br, 2H), 2.54 (br, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.02 (br, 3H), 1.80 (br, 1H), 1.70 (br, 1H).

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.9 min.

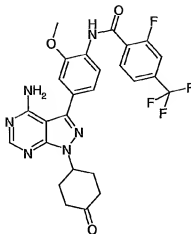
MS: MH<sup>+</sup> 513

Example 868: *Cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carboxamide triacetate



- To a mixture of *cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carbonitrile triacetate (0.18 g, 0.00025 mol) in dioxane (2 mL) were added a 2N aqueous solution of sodium hydroxide (1.25 mL, 0.0025 mol) and water (0.75 mL). The mixture was stirred at room temperature for 2 minutes under the atmosphere of nitrogen before adding 30 % hydrogen peroxide solution (0.2 mL). The mixture was refluxed for 5 hours, then stirred at room temperature for 18 hours. More 30 % hydrogen peroxide solution (0.2 mL) was added to the mixture before refluxing for additional 6 hours, then stirred at room temperature for 2 days. The organic solvent was removed under reduced pressure, and 5 % citric acid solution was added to maintain pH 7. The aqueous layer was removed under reduced pressure, and the crude was purified by RP-HPLC (Hypersilprep HS C18, 8 $\mu$ m, 250 x 21.1 mm; 5% - 100 % over 25 min with 0.1 M ammonium acetate, 21mL/min) to give *cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carboxamide triacetate (0.11 g, 0.00015 mol).
- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  8.30 (s, 1H), 8.15 (s, 1H), 8.00 (m, 3H), 7.75 (m, 1H), 7.70(m, 2H), 7.60 (d, 1H), 7.35 (br, 1H), 4.80 (br, 1H), 2.50 (br, 2H), 2.40 (br, 4H), 2.25 (br, 4H), 2.15 (s, 3H), 2.10 (br, 3H), 1.90 (s, 9H), 1.70 (br, 2H), 1.60 (br, 2H).
- RP-HPLC (Delta Pak C18, 5 $\mu$ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.2 min.
- MS: MH<sup>+</sup> 567

- Example 869: N1-{4-[4-Amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide



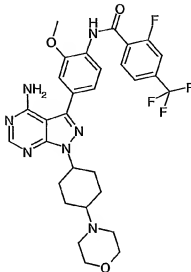
A solution of 2-fluoro-4-trifluoromethyl-1-benzenecarbonyl chloride (0.87 g, 3.83 mmol) in dichloromethane (5 mL) was added into a mixture of pyridine (15 mL) and 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-cyclohexanone (1.00 g, 2.56 mmol) in dichloromethane (5 mL) at 0°C over 5 minutes. The mixture was stirred at 0°C for 10 minutes and at ambient temperature overnight. The solvent was removed under reduced pressure. The residue was partitioned between water and dichloromethane. The dichloromethane layer was washed with saturated aqueous ammonium chloride twice and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography on silica using Isco system to provide N1-(4-[4-amino-1-(4-oxocyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-trifluoromethylbenzamide (0.95 g, 1.76 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.90 (dd, 1H), 8.30(d, 1H), 8.28 (s, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.34 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 5.27 (m, 1H), 3.94 (s, 3H), 2.70 (m, 2H), 2.47 (m, 4H), 2.17 (m, 2H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 $\mu$ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R<sub>t</sub> 9.23 min. MS: MH<sup>+</sup> 543.

20

Example 870: Cis-N1-(4-[4-amino-1-(4-morpholinocyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-trifluoromethylbenzamide; and

Example 871: Trans-N1-(4-[4-amino-1-(4-morpholinocyclohexyl)-1H-pyrazolo[3,4-

*d*[pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide



Morpholine (0.08 mL, 0.93 mmol) was added into a mixture of *N*1-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.42 g, 0.78 mmol) and acetic acid (0.11 mL, 1.86 mmol) in dichloroethane (25 mL). The mixture was stirred at ambient temperature for 10 minutes. Sodium triacetoxyborohydride (0.23 g, 1.09 mmol) was added and the mixture was stirred at ambient temperature overnight. Water (6 mL) was added followed by sodium bicarbonate (0.38 g, 4.53 mmol). The mixture was stirred for 1 hour and the organic layer was separated. The aqueous layer was extracted with dichloromethane (20 mL). The combine organics were dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography on silica using Isco system to provide *cis*-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.23 g, 0.37 mmol) and *trans*-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.09 g, 0.14 mmol) as white solids.

Data for *cis*-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.91 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 4.83 (m, 1H),

3.94 (s, 3H), 3.62 (br, 4H), 1.57-2.55 (m, 10H); MS:  $MH^+$  614.

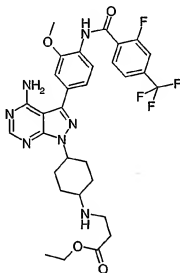
Data for trans-N1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-

trifluoromethylbenzamide:  $^1H$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  9.90 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 4.67 (m, 1H), 3.94 (s, 3H), 3.59 (br, 4H), 1.48-2.69 (m, 10H); MS:  $MH^+$  614.

Example 872: *Cis*-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-

trifluoromethylbenzoyl]amino)-3-methoxyphenyl)-1H-pyrazolo[3,4-  
d]pyrimidin-1-yl]cyclohexyl)amino)propanoate; and

Example 873: *Trans*-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-  
trifluoromethylbenzoyl]amino)-3-methoxyphenyl)-1H-pyrazolo[3,4-  
d]pyrimidin-1-yl]cyclohexyl)amino)propanoate



15

A similar procedure to the preparation of *cis*-N1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide and *trans*-N1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide yielded *cis*-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino)-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]cyclohexyl)amino)propanoate and *trans*-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino)-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-

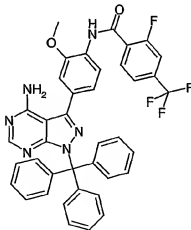
20

1-yl]cyclohexyl]amino)propanoate as white solids.

Data for cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl]amino)propanoate: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.90 (dd, 1H), 8.30(d, 1H), 8.23 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 4.37 (m, 1H), 4.08 (q, 2H), 3.94 (s, 3H), 2.76 (m, 2H), 2.32 (m, 2H), 1.88 (m, 2H), 1.67 (m, 4H), 1.16 (t, 3H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 $\mu$ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R<sub>t</sub> 7.92 min. MS: MH<sup>+</sup> 644.

Data for trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl]amino)propanoate: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.89 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (d, 1H), 6.90 (br, 2H), 4.68 (m, 1H), 4.08 (q, 2H), 3.94 (s, 3H), 2.82 (m, 2H), 2.46 (m, 5H), 1.91-2.07 (m, 6H), 1.18 (t, 3H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 $\mu$ m, 100A, 250x4.6mm, 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R<sub>t</sub> 7.69 min. MS: MH<sup>+</sup> 644.

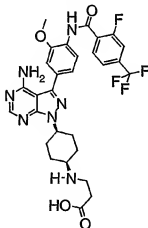
Example 874: N1-[4-(4-Amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide



A mixture of 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.10 g, 0.19 mmol), N1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-trifluoromethylbenzamide (0.13 g, 0.29 mmol),

- tetrakis(triphenylphosphine)palladium(0) (0.01 g, 0.01 mmol) and sodium carbonate monohydrate (0.06 mg, 0.48 mmol) in water (2 mL) and ethylene glycol dimethyl ether (4 mL) was heated at 85°C overnight. The solvents were removed under reduced pressure. Water was added into the residue and the mixture was extracted with ethyl acetate three times. The combined organics were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield a brown solid which was purified by flash column chromatography on silica using Isco system to provide *N*1-[4-(4-amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.12 g, 0.17 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.89 (dd, 1H), 8.25(d, 1H), 8.28 (s, 1H), 8.00 (t, 1H), 7.94 (s, 1H), 7.88 (d, 1H), 7.73 (d, 1H), 7.24 (m, 15H), 3.90 (s, 3H); MS: MH<sup>+</sup> 689.

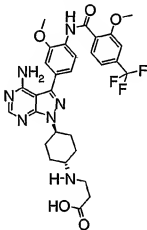
- 15 Example 875: *Cis*-3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl)amino}propanoic acid



- A mixture of *cis*-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl)amino}propanoate (0.23 g, 0.36 mmol), p-dioxane (15 mL), potassium hydroxide (0.10 g, 1.81 mmol) and water (1.5 mL) were heated at 80°C for 3 hours. The solvents were evaporated and the residue was purified by preparative HPLC to yield *cis*-3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-

methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid (0.11 g, 0.18 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.91 (dd, 1H), 8.31 (d, 1H), 8.25 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.35 (s, 1H), 7.32 (s, 1H), 6.89 (br, 2H), 4.79 (m, 1H), 3.95 (s, 3H), 2.46-3.00 (m, 7H), 2.29 (m, 2H), 1.91 (m, 2H), 1.80 (m, 2H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 $\mu$ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R<sub>f</sub> 6.06 min. MS: MH<sup>+</sup> 616.

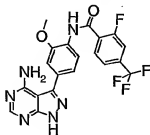
Example 876: Trans-3-({4-[4-amino-3-(3-methoxy-4-{[2-methoxy-4-trifluoromethylbenzoyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid



A mixture of trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate (0.04 g, 0.06 mmol), p-dioxane (4 mL), potassium hydroxide (0.02 g, 0.31 mmol), a trace amount of methanol and water (0.4 mL) were heated at 80°C for 1 hour. The mixture was stirred at ambient temperature overnight and at 80°C for 4 hours. The solvents were evaporated and the residue was purified by preparative HPLC to yield trans-3-({4-[4-amino-3-(3-methoxy-4-{[2-methoxy-4-trifluoromethylbenzoyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid (0.04 g, 0.06 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  10.72 (s, 1H), 8.61(d, 1H), 8.28 (d, 1H), 8.24 (s, 1H), 7.61(s, 1H), 7.53 (d, 1H), 7.33 (s, 1H), 7.29 (d, 1H), 4.72 (m, 1H), 4.20 (s, 3H), 4.05 (s, 3H), 1.44-3.61 (m, 13H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 $\mu$ m, 100A,

250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min,  
1mL/min)  $R_t$  6.36 min. MS:  $MH^+$  628.

Example 877: *N*1-[4-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-  
methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide

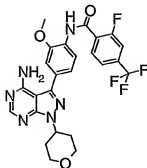


A mixture of *N*1-[4-(4-amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (2.10 g, 1.75 mmol), 6 N aqueous hydrochloric acid (10 mL), *p*-dioxane (10 mL) and ethanol (8 mL) was heated at 50°C for 6 hours. The mixture was filtered and the solid was washed with ethanol, dried in a vacuum oven over the weekend, and purified by flash column chromatography on silica to provide *N*1-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.35 g, 0.78 mmol). The filtrate was concentrated and purified by flash column chromatography on silica and preparative HPLC to provide the same product *N*1-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.67 g, 1.51 mmol) as a white solid:  $^1H$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  13.58 (s, 1H), 9.90 (dd, 1H), 8.30(d, 1H), 8.23 (s, 1H), 8.05 (t, 1H), 7.90 (d, 1H), 7.75 (d, 1H), 7.36 (s, 1H), 7.24 (d, 1H), 3.94 (s, 3H); MS:  $MH^+$  447.

Example 878: *N*1-[4-(4-Amino-1-tetrahydro-2*H*-4-pyran-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide

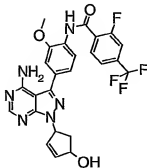


-736-



Diethyl azodicarboxylate (0.07 mL, 0.45 mmol) was added into a mixture of  
*N*1-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-  
 trifluoromethylbenzamide (0.10 g, 0.22 mmol), triphenylphosphine (0.12 g, 0.45  
 5 mmol) and tetrahydro-4*H*-pyran-4-ol (0.04 g, 0.34 mmol) in tetrahydrofuran (5 mL)  
 and the mixture was stirred at ambient temperature overnight. Tetrahydro-4*H*-pyran-  
 4-ol (0.01 g, 0.11 mmol), triphenylphosphine (0.04 g, 0.15 mmol) and diethyl  
 azodicarboxylate (0.02 mL, 0.15 mmol) were added and the mixture was stirred at  
 ambient temperature for 5 hours. The solvents were evaporated and the residue was  
 10 purified by preparative HPLC to yield *N*1-[4-(4-amino-1-tetrahydro-2*H*-4-pyran-yl-  
 1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-  
 trifluoromethylbenzamide (0.03 g, 0.06 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>,  
 400MHz)  $\delta$  9.91 (dd, 1H), 8.30(d, 1H), 8.25 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75  
 (d, 1H), 7.34 (s, 1H), 7.31 (d, 1H), 6.90 (br, 2H), 4.95 (m, 1H), 4.02 (m, 2H), 3.95  
 15 (s, 3H), 3.56 (t, 2H), 2.22 (m, 2H), 1.89 (m, 2H); MS: MH<sup>+</sup> 531.

Example 879: *N*1-[4-[4-Amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-  
*d*]pyrimidin-3-yl]-2-methoxyphenyl]-2-fluoro-4-  
 trifluoromethylbenzamide



20

A. 4-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-

## cyclopenten-1-ol

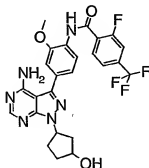
A mixture of tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol), 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.30 g, 1.14 mmol) and dimethyl sulfoxide (3 mL) was stirred at ambient temperature in the dark for 2 minutes and cooled to 0°C. A solution of 2,4*a*-dihydro-1*aH*-cyclopenta[*b*]oxirene (0.14 g, 1.72 mmol) in tetrahydrofuran (3 mL) was added into the mixture at 0°C and stirred at 0°C for 3 hours. The mixture was stirred at ambient temperature overnight and purified by preparative HPLC to yield 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol (0.24 g, 0.70 mmol) as a white solid: RP-HPLC (Hitachi HPLC, Hypersil C18, 5µm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) *R*<sub>t</sub> 4.23 min. MS: *MH*<sup>+</sup> 344.

B. *N*1-{4-[4-Amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

A mixture of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol (0.12 g, 0.35 mmol), *N*1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-trifluoromethylbenzamide (0.23 g, 0.53 mmol), tetrakis(triphenyl-phosphine)palladium(0) (0.02 g, 0.02 mmol) and sodium carbonate monohydrate (0.11 g, 0.88 mmol) was heated in a mixture of ethylene glycol dimethyl ether (6 mL) and water (3 mL) at 85°C for 6 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC to yield *N*1-{4-[4-amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.18 g, 0.34 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.89 (dd, 1H), 8.31 (d, 1H), 8.26 (s, 1H), 8.00 (t, 1H), 7.88 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (d, 1H), 6.90 (br, 2H), 6.09 (d, 1H), 5.93 (d, 1H), 5.76 (m, 1H), 5.31 (m, 1H), 4.74 (m, 1H), 3.94 (s, 3H), 2.84 (m, 1H), 2.02 (m, 1H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5µm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) *R*<sub>t</sub> 8.50 min. MS:

MH<sup>+</sup> 529.

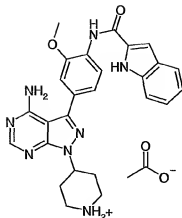
Example 880: N1-{4-[4-Amino-1-(3-hydroxycyclopentyl)-1H-pyrazolo[3,4-  
d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-  
trifluoromethylbenzamide



A mixture of N1-{4-[4-amino-1-(4-hydroxy-2-cyclopentyl)-1H-pyrazolo[3,4-  
d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-  
trifluoromethylbenzamide (0.10 g, 0.19 mmol) and 10% palladium on carbon (0.03  
g) in ethanol (10 mL) was stirred at ambient temperature under one atmosphere of  
hydrogen overnight. The mixture was filtered and the filtrate was purified by  
preparative HPLC to yield N1-{4-[4-amino-1-(3-hydroxycyclopentyl)-1H-  
pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-  
trifluoromethylbenzamide (0.07 g, 0.13 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>,  
400MHz)  $\delta$  9.91 (dd, 1H), 8.31(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75  
(d, 1H), 7.34 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 5.17 (m, 1H), 4.97 (m, 1H), 4.22  
(m, 1H), 3.94 (s, 3H), 1.79-2.41 (m, 6H); MS: MH<sup>+</sup> 531.

Example 881: 4-(4-Amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-  
1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate

-739-

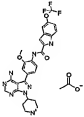
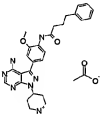
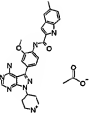
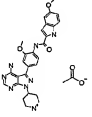
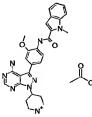


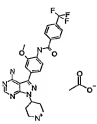
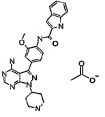
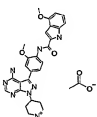
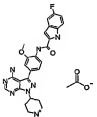
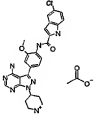
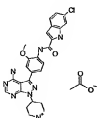
Oxalyl chloride (0.06 mL, 0.60 mmol) was added into a solution of indole-2-carboxylic acid (0.88 g, 0.546 mmol) in dichloromethane (5 mL) and tetrahydrofuran (5 mL) at 0°C. *N,N*-dimethylformamide (3 drops from 0.1 mL syringe) was added and the mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. The solvents and excess of reagents were evaporated under reduced pressure. The residue was taken into dichloromethane (2 mL) and the resulting solution (1.25 mL) was added into a solution of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinecarboxylate (0.12 g, 0.27 mmol) and pyridine (0.4 mL) in dichloromethane (1 mL). The mixture was stirred at ambient temperature for 2 hours. Trifluoroacetic acid (1 mL) was added and the mixture was stirred at ambient temperature for 2 hours. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC to yield 4-(4-amino-3-{4-[(1H-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)hexahydropyridinium acetate (0.07 g, 0.14 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  11.85 (br, 1H), 9.45 (s, 1H), 8.24 (d, 1H), 8.12 (d, 1H), 7.68(d, 1H), 7.48 (d, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.30 (d, 1H), 7.24 (t, 1H), 7.09 (t, 1H), 4.77 (m, 1H), 3.97 (s, 3H), 3.11 (m, 2H), 2.68 (m, 2H), 2.09 (m, 2H), 1.89 (s, 3H), 1.84 (m, 2H); MS: MH<sup>+</sup> 483.

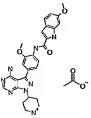
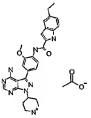
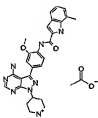
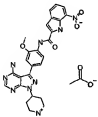
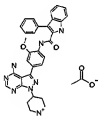
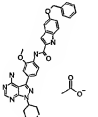
#### Example 882-902:

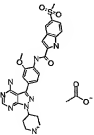
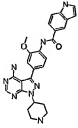
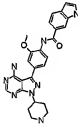
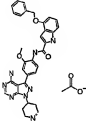
The same protocol as was used to prepare 4-(4-amino-3-{4-[(1H-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)hexahydropyridinium acetate (Example 881) was used to prepare Examples 882-

902.

Structure	MS: MH+	HPLC Rt (min) (Hypersil C18, 5µm, 100Å, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)	Example No.
	567	6.97	882
	486	5.89	883
	497	6.28	884
	513	5.61	885
	497	6.39	886

	512	6.22	887
	483	5.73	888
	513	7.78	889
	501	8.23	890
	517	8.7	891
	517	8.73	892

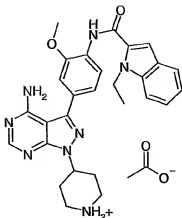
	513	7.83	893
	511	9.07	894
	497	8.37	895
	528	7.9	896
	559	9.5	897
	589	7.45	898

	561	4.52	899
	483	6.35	900
	483	7.05	901
	589	6.63	902

Example 903: 4-[4-Amino-3-(4-[[1-ethyl-1H-2-indolyl]carbonyl]amino)-3-methoxyphenyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl]hexahydropyridinium acetate



-744-

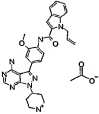
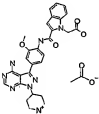
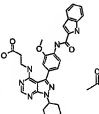
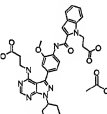
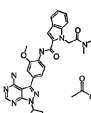


- Sodium hydride, 60% suspension in mineral oil (0.006 g, 0.15 mmol) was added into the solution of *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1*H*-2-indolecarboxamide (0.08 g, 0.14 mmol) in *N,N*-dimethylformamide (1.0 mL) at 0°C. The mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. A solution of ethyl iodide (0.02 g, 0.14 mmol) in *N,N*-dimethylformamide (0.5 mL) was added in and the mixture was stirred at ambient temperature overnight. Ethyl iodide (0.01 g, 0.07 mmol) was added in and the mixture was stirred at ambient temperature overnight.
- Trifluoroacetic acid (3 mL) was added and the mixture was stirred at ambient temperature for 24 hours. The solvents and excess reagents were evaporated under reduced pressure and the residue was purified by preparative HPLC to yield 4-[4-amino-3-(4-[(1-ethyl-1*H*-2-indolyl)carbonyl]amino)-3-methoxyphenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate (0.05 g, 0.09 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 9.43 (s, 1H), 8.27 (s, 1H), 8.14 (d, 1H), 7.71(d, 1H), 7.61 (d, 1H), 7.34 (s, 2H), 7.31 (t, 2H), 7.15 (t, 1H), 4.96 (m, 1H), 4.62 (q, 2H), 3.96 (s, 3H), 3.00 (m, 2H), 2.28 (m, 2H), 2.03 (m, 2H), 1.91 (s, 3H), 1.33 (t, 3H); MS: MH<sup>+</sup> 511.

20

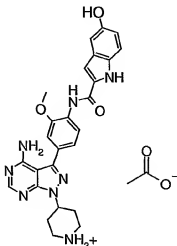
Example 904 to 908:

- The same protocol that was used to prepare 4-[4-amino-3-(4-[(1-ethyl-1*H*-2-indolyl)carbonyl]amino)-3-methoxyphenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate (Example 903) was used to prepare Examples 904-908.

Structure	MS: MH+	HPLC Rt (min) (Hypersil C18, 5µm, 100Å, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)	Example No.
	523	9.12	904
	540	6.03	905
	555	5.30	906
	627	6.55	907
	568	7.33	908

Example 909: N2-4-[4-Amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-

methoxyphenyl-5-hydroxy-1*H*-2-indolecarboxamide acetate salt

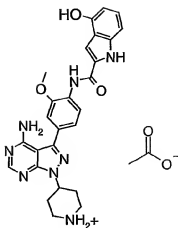


A mixture of *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-5-(benzyloxy)-1*H*-2-indolecarboxamide (0.08 g, 0.14 mmol), 10% palladium on carbon (0.03 g) and trifluoroacetic acid (a drop) in ethanol (12 mL) and tetrahydrofuran (12 mL) was hydrogenated under one atmosphere of hydrogen overnight. The mixture was filtered and the filtrate was purified by preparative HPLC to yield *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-5-hydroxy-1*H*-2-indolecarboxamide acetate salt (0.02 g, 0.03 mmol) as a white solid:

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  11.55 (s, 1H), 9.29 (s, 1H), 8.88 (s, 1H), 8.28 (s, 1H), 8.18(d, 1H), 7.31 (m, 3H), 7.18 (s, 1H), 6.94 (s, 1H), 6.78 (dd, 1H), 5.06 (m, 1H), 3.97 (s, 3H), 3.44 (m, 2H), 3.17 (m, 2H), 2.39 (m, 2H), 2.11 (m, 2H), 1.91 (s, 3H); MS: MH<sup>+</sup> 499.

Example 910: *N*2-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-4-hydroxy-1*H*-2-indolecarboxamide acetate salt

-747-

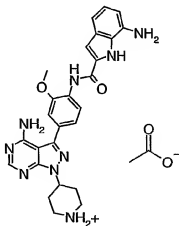


The same protocol that was used to prepare *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-5-hydroxy-1*H*-2-

indolecarboxamide acetate salt was used to prepare *N*2-4-[4-amino-1-(4-piperidyl)-

- 5 1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-4-hydroxy-1*H*-2-indolecarboxamide acetate salt. RP-HPLC (Hitachi HPLC, Hypersil C18, 5 $\mu$ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)  $R_t$  4.60 min. MS:  $MH^+$  499.

- 10 Example 911: *N*2-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-7-amino-1*H*-2-indolecarboxamide acetate salt

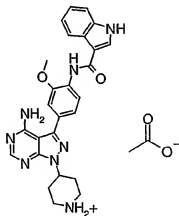


Sodium dithionite (0.07 g, 0.41 mmol) was added into a hot solution of *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-7-

- 15 nitro-1*H*-2-indolecarboxamide acetate salt (0.04 g, 0.07 mmol) in water (2 mL) and ethanol (2 mL). The mixture was allowed to cool to ambient temperature. One drop

of concentrated hydrochloric acid was added and the mixture was purified by preparative HPLC to yield *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-7-amino-1*H*-2-indolecarboxamide acetate salt (0.004 g, 0.01 mmol) as a white solid: RP-HPLC (Hitachi HPLC, Hypersil C18, 5  $\mu$ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) *R*<sub>t</sub> 6.60 min. MS: *M*H<sup>+</sup> 498.

Example 912: *N*3-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-3-indolecarboxamide acetate salt



10

A. *N*3-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-3-indolecarboxamide

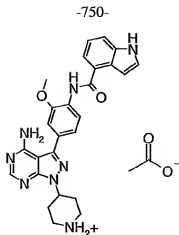
Oxalyl chloride (0.07 mL, 0.79 mmol) was added into a solution of indole-3-carboxylic acid (0.12 g, 0.72 mmol) in dichloromethane (4 mL) and tetrahydrofuran (3 mL) at 0°C. *N,N*-dimethylformamide (3 drops from 0.1 mL syringe) was added and the mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. The solvents and excess of reagents were evaporated under reduced pressure. The residue was taken into dichloromethane (2 mL) and the resulting solution (1.5 mL) was added into a solution of 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.09 g, 0.36 mmol) and pyridine (1 mL) in dichloromethane (2 mL). The mixture was stirred at ambient temperature overnight. The acid chloride solution in dichloromethane (0.3 mL) was added in and the mixture was stirred overnight. Water (a drop) was added in. The volatile components were evaporated under reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate.

The organic extracts were combined and washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. The mixture was filtered and the solvent of the filtrate was evaporated to yield the crude which was purified by flash column chromatography on silica using n-heptane: ethyl acetate (2/1) as a mobile phase to yield *N*3-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-3-indolecarboxamide (0.11 g, 0.28 mmol) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) δ 8.65 (m, 3H), 8.13 (d, 1H), 7.95 (s, 1H), 7.50 (m, 2H), 7.33(m, 3H), 4.02 (s, 3H), 1.36 (s, 12H); MS: MH<sup>+</sup> 393.

B. *N*3-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-3-indolecarboxamide acetate salt

A mixture of *N*3-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-3-indolecarboxamide (0.11 g, 0.28 mmol), 3-iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloric salt (0.10 g, 0.27 mmol), tetrakis(triphenyl-phosphine)palladium(0) (0.02 g, 0.02 mmol) and sodium carbonate monohydrate (0.13 g, 1.07 mmol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 85°C overnight under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC to yield *N*3-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-3-indolecarboxamide acetate salt (0.09 g, 0.16 mmol) as a white solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ 11.83 (br, 1H), 8.92 (s, 1H), 8.31 (m, 3H), 8.14 (dd, 1H), 7.50 (dd, 1H), 7.31 (m, 2H), 7.20 (m, 2H), 4.82 (m, 1H), 3.99 (s, 3H), 3.16 (m, 2H), 2.73 (m, 2H), 2.15 (m, 2H), 1.91 (s, 3H), 1.88 (m, 2H); MS: MH<sup>+</sup> 483.

Example 913: *N*4-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-4-indolecarboxamide acetate salt



The same protocol that prepare *N*3-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-3-indolecarboxamide acetate salt was used to *N*4-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-4-indolecarboxamide acetate salt. RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) *R*<sub>t</sub> 4.80 min. MS: *M*H<sup>+</sup> 483.

Example 914: *trans*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A. 1-methyl-1*H*-2-indolecarbonyl chloride

A suspension of 1-methylindole-2-carboxylic acid (9.87 g, 56.4 mmol) in dichloro-methane (150 mL) was reacted with oxalyl chloride (8.58 g, 67.63 mmol). DMF was added (0.2 mL), upon which a vigorous reaction transpired. The mixture was stirred at ambient temperature for four hours. The solvent was removed *in vacuo* to give 1-methyl-1*H*-2-indolecarbonyl chloride (10.69 g, 98%) as a light yellow solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) δ 7.70 (d, 1H), 7.66 (s, 1H), 7.44 (t, 1H), 7.35 (d, 1H), 7.18 (t, 1H), 3.98 (s, 3H).

B. *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide

To a solution containing 1-methyl-1*H*-2-indolecarbonyl chloride (5.44 g, 0.0281 mol) and 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (7.00 g, 0.0281 mol) in anhydrous dichloromethane (150 mL), *N*-ethyl-*N*,*N*-

diisopropylamine (4.9 mL, 0.0309 mol) was added dropwise at 0°C and the resulting solution was stirred at ambient temperature under an atmosphere of nitrogen for 18 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between water (150 mL) and ethyl acetate (150 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:6) as mobile phase to yield *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (8.0 g, 0.0197 mol) as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz)  $\delta$  9.35 (s, 1H), 8.03 (d, 1H), 7.69 (d, 1H), 7.57 (d, 1H), 7.33 (m, 3H), 7.29 (s, 1H), 7.14 (t, 1H), 4.02 (s, 3H), 3.91 (s, 3H), 1.31 (s, 12H). TLC (ethyl acetate / heptane 1:3) R<sub>f</sub> 0.44

C. *trans*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A suspension of *trans*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.227 mmol) in ethylene glycol dimethyl ether (8 mL) was treated with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.097g, 0.238 mmol), tetrakis(triphenylphosphine)palladium (0.016g, 0.014 mmol), and a solution of sodium carbonate (0.057g, 0.538 mmol) in water (4 mL). The reaction mixture was stirred for 21.5 h at 80°C. The precipitate was filtered, and the organic layer was evaporated under reduced pressure. Dichloromethane (15 mL) was added and the layers were partitioned. The aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a 10% methanol in dichloromethane to 50% methanol in dichloromethane step gradient on Sq 16x ISCO CombiFlash. The column afforded 0.083 g (68%) of *trans*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO)



5      $\delta$  9.4316 (s, 1H), 8.2427 (s, 1H), 8.1207-8.1003 (d, 1H,  $J = 8.16$  Hz), 7.7173-7.6974 (d, 1H,  $J = 7.96$  Hz), 7.5979-7.5769 (d, 1H,  $J = 8.4$  Hz), 7.3507-7.2758 (m, 4H), 7.1695-7.1321 (t, 1H), 4.6893-4.6324 (m, 1H), 4.0400 (s, 3H), 3.9571 (s, 3H), 2.5 (m, 3H), 2.4055-2.3279 (m, 5H), 2.1606 (s, 3H), 2.1094-1.9367 (m, 6H), 1.5214-1.4624 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3 $\mu$ m particle size, 33 x 4.6mm; 70 % 50 mM ammonium Acetate in Water to 95% Acetonitrile over 6 min, 0.8 to 0.5 mL/min)  $R_t$  2.12 min (100%),  $M^+$  594.3.

10     Example 915: *N*2-{4-[4-amino-1-(2-amino-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

15     Example 916: *N*2-(4-{4-amino-1-[2-(methylamino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

20     Example 917: *N*2-(4-{4-amino-1-[2-(dimethylamino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

25     Example 918: *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

30     Example 919: *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

35     Example 920: *N*2-{4-[4-amino-1-(2-morpholino-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

40     Example 921: *N*2-[4-(4-amino-1-{2-[(2-hydroxyethyl)amino]-4-pyridyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-

## indolecarboxamide

Example 922: *N*2-(4-{4-amino-1-[2-(aminomethyl)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-

5 indolecarboxamide

Example 923: *N*2-(4-{4-amino-1-[2-(aminocarbonyl)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-

indolecarboxamide

10

Example 924: 3-morpholino-1-(2-morpholino-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

Example 925: *N*2-{4-[4-amino-1-(4-amino-2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

15

Example 926: *N*2-{4-[4-amino-1-(2-oxo-1,2-dihydro-4-pyridinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

20

Example 927: *N*2-{4-[4-amino-1-(4-morpholino-2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

25 Example 928: *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)-2-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

Example 929: *N*2-[4-(4-amino-1-{4-[(2-hydroxyethyl)amino]-2-pyridyl})-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

30

Example 930: *N*2-{4-[4-amino-1-(6-amino-3-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-

3-yl]-2-methoxyphenyl)-1-methyl-1*H*-2-indolcarboxamide

Example 931: *N*2-{4-[4-amino-1-(6-morpholino-3-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-

5 indolcarboxamide

Example 932: *N*2-(4-{4-amino-1-[6-(4-methylpiperazino)-3-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolcarboxamide

10

Example 933: *Cis*-4-[4-(4-amino-3-{3-fluoro-4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexyl]-2-piperazinone

15 Example 934: *Trans*-4-[4-(4-amino-3-{3-fluoro-4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexyl]-2-piperazinone

Example 935: *Cis*-4-[4-(4-amino-3-{4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexyl]-2-piperazinone

20

Example 936: *Trans*-4-[4-(4-amino-3-{4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexyl]-2-piperazinone

25

Example 937: *R*-*N*2-(4-{4-amino-1-[1-(1-methoxy-1-methylethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

30

Example 938: *S*-*N*2-(4-{4-amino-1-[1-(1-methoxy-1-methylethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 939: R/S-N2-(4-{4-amino-1-[1-(1-methoxy-1-methylethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

5

Example 940: R-N2-(4-{4-amino-1-[1-(3-methoxypropyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

10 Example 941: S-N2-(4-{4-amino-1-[1-(3-methoxypropyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

15 Example 942: R/S-N2-(4-{4-amino-1-[1-(3-methoxypropyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

20 Example 943: R-N2-(4-{4-amino-1-[1-(2-hydroxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

25 Example 944: S-N2-(4-{4-amino-1-[1-(2-hydroxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

25

Example 945: R/S-N2-(4-{4-amino-1-[1-(2-hydroxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

30 Example 946: R-N2-(4-{4-amino-1-[1-(2-{1,3-dihydroxypropyl})-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 947: S-N2-(4-{4-amino-1-[1-(2-{1,3-dihydroxypropyl})-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

- 5    Example 948: R/S-N2-(4-{4-amino-1-[1-(2-{1,3-dihydroxypropyl})-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

- 10    Example 949: R-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino]acetonitrile

- 15    Example 950: S-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino]acetonitrile

- 20    Example 951: R/S-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino]acetonitrile

Example 952: R-N2-(4-{4-amino-1-[1-(2-(methylsulfonyl)ethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

- 25    Example 953: S-N2-(4-{4-amino-1-[1-(2-(methylsulfonyl)ethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

- 30    Example 954: R/S-N2-(4-{4-amino-1-[1-(2-(methylsulfonyl)ethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 955: R-N-methoxy-3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-

yl)amino]phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboximidamide

5 Example 956: S-N-methoxy-3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboximidamide

10 Example 957: R/S-N-methoxy-3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboximidamide

15 Example 958: R-N2-(4-4-amino-1-[1-(1-2,2,2-trifluoroethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-ylphenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 959: S-N2-(4-4-amino-1-[1-(1-2,2,2-trifluoroethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-ylphenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

20 Example 960: R/S-N2-(4-4-amino-1-[1-(1-2,2,2-trifluoroethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-ylphenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

25 Example 961: N2-{4-[4-amino-1-(1H-4-imidazolylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

30 Example 962: N2-(4-{4-amino-1-[1H-4-(2-methyl-imidazolyl)methyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 963: N2-(4-{4-amino-1-[1H-4-(2-amino-imidazolyl)methyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 964: N2-4-[4-amino-1-(1H-4-imidazolyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl-5,7-dimethyl-1,3-benzoxazol-2-amine

- 5    Example 965: N2-4-{4-amino-1-[1H-4-(2-amino-imidazolyl)]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 966: N2-4-{4-amino-1-[1H-4-(2-methyl-imidazolyl)]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

10

Example 967: 1-(4-{4-amino-3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}piperidino)-2-methyl-2-(methylamino)-1-propanone

- 15    Example 968: 1-[4-(4-amino-3-{4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino)-2-methyl-2-(methylamino)-1-propanone

Example 969: 1-[4-(4-amino-3-{4-[(5-ethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino)-2-methyl-2-(methylamino)-1-propanone

20

Example 970: 1-[4-(4-amino-3-{4-[(5-chloro-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino)-2-methyl-2-(methylamino)-1-propanone

25

Example 971: {4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}(1H-4-pyrazolyl)methanone

- 30    Example 972: 1-(4-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoyl}-1H-1-pyrazolyl)-1-ethanone

Example 973: {4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-

yl]phenyl}(1-methyl-1*H*-4-pyrazolyl)methanone

Example 974: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(1-benzyl-1*H*-4-pyrazolyl)methanone

5

Example 975: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(1-benzoyl-1*H*-4-pyrazolyl)methanone

10

Example 976: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(5-isoxazolyl)methanone

Example 977: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(3-methyl-5-isoxazolyl)methanone

15

Example 978: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(3-phenyl-5-isoxazolyl)methanone

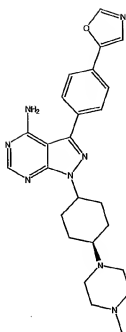
Example 979: *N*5-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-3-phenyl-5-isoxazamine

20

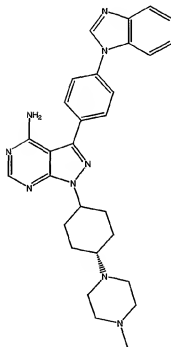
Example 980: *N*5-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-3-(trifluoromethyl)-5-isoxazamine



-760-

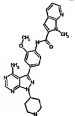
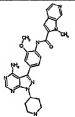
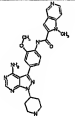
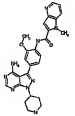
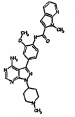
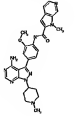


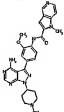
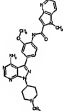
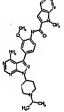
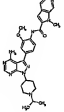
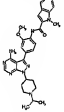
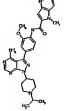
Example 981

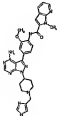
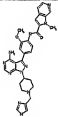
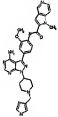
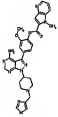
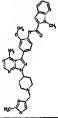
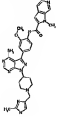


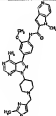
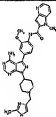
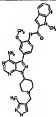
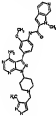
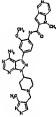
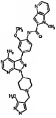
Example 982

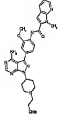
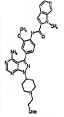
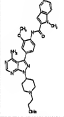
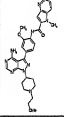
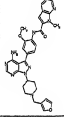
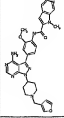
Other Examples include the following compounds:

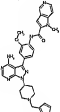
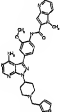
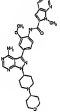
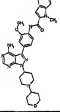
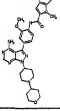
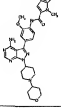
Structure	Name
	N2-[4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

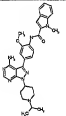
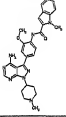
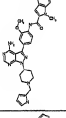
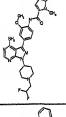
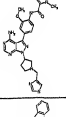
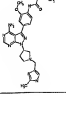
Structure	Name
	N2-[4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

Structure	Name
	N2-(4-(4-amino-1-[(1-(1H-4-imidazolyl)methyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-(4-(4-amino-1-[(1-(1H-4-imidazolyl)methyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-(4-(4-amino-1-[(1-(1H-4-imidazolyl)methyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-(4-(4-amino-1-[(1-(1H-4-imidazolyl)methyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-[4-(4-amino-1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-[4-(4-amino-1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

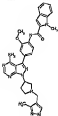
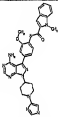
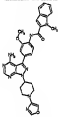
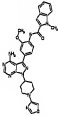
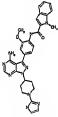
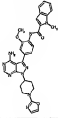
Structure	Name
	N2-[4-(4-amino-1-{1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

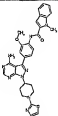
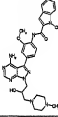
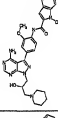
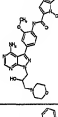
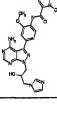
Structure	Name
	N2-(4-[4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-(4-[4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-(4-[4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-(4-[4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-(4-[4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-(4-[4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

Structure	Name
	N2-[4-[4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-[4-[4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-tetrahydro-2H-4-pyranyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-tetrahydro-2H-4-pyranyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-tetrahydro-2H-4-pyranyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-[4-[4-amino-1-(1-tetrahydro-2H-4-pyranyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

Structure	Name
	N2-[4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-[4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-[4-[4-amino-1-[1-(1H-2-pyrrolylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-[4-[4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-[4-[4-amino-1-[1-(1H-4-imidazolylmethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-[4-[4-amino-1-[1-(2-methyl-1H-4-imidazolylmethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide



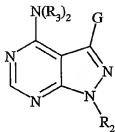
Structure	Name
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]tetrahydro-1H-3-pyrrlyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1H-4-imidazolyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1,3-oxazol-4-yl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1,3-thiazol-4-yl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1H-2-imidazolyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1,3-oxazol-2-yl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide

Structure	Name
	N2-[4-[4-amino-1-[1-(1,3-thiazol-2-yl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-[4-[4-amino-1-[2-hydroxy-3-(4-methylpiperazino)propyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-[4-[4-amino-1-[2-hydroxy-3-piperidinopropyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-[4-[4-amino-1-[2-hydroxy-3-morpholinopropyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-[4-[4-amino-1-[2-hydroxy-3-(1H-1-imidazolyl)propyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide

## CLAIMS

We claim:

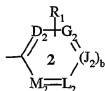
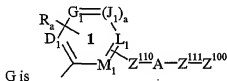
- 5 1. A compound of Formula (I)



(I)

10

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

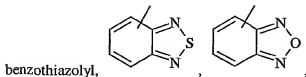


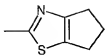
15

where  $Z^{100}$  is

or a group optionally substituted with  $R_1$  selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxaliny, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,

20





, thiazolyl, benzofuranyl, 2,3-

dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl,

tetrahydrofuranlyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl,

H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl,

5 indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-

dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

$Z^{110}$  is a covalent bond, or an optionally substituted ( $C_1-C_6$ ) which is

optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ ,  $COOH$ , substituted or unsubstituted amino and substituted or unsubstituted phenyl;

$Z^{111}$  is a covalent bond, an optionally substituted ( $C_1-C_6$ ) or an optionally

substituted  $-(CH_2)_n$ -cycloalkyl- $(CH_2)_m$ -; where the optionally substituted groups are optionally substituted with one or more

substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ ,  $COOH$ , substituted or unsubstituted amino and substituted or unsubstituted phenyl;

$R_a$  and  $R_1$  each represent one or more substituents for each occurrence

independently selected from the group consisting of hydrogen,

halogen,  $-CN$ ,  $-NO_2$ ,  $-C(O)OH$ ,  $-C(O)H$ ,  $-OH$ ,  $-C(O)O$ -alkyl,  $-C(O)O$ -aryl,  $-C(O)O$ -heteroaryl,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl,

trifluoromethylcarbonylamino, trifluoromethylsulfonamido,

substituted or unsubstituted alkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy,

substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted

arylalkoxy, substituted or unsubstituted alkyl- $S(O)_p$ -, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl- $S(O)_p$ -,

- substituted or unsubstituted heteroaryl-S(O)<sub>p</sub>-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z<sup>105</sup>-C(O)N(R)<sub>2</sub>-, -Z<sup>105</sup>-N(R)-C(O)-Z<sup>200</sup>-, -Z<sup>105</sup>-N(R)-S(O)<sub>2</sub>-Z<sup>200</sup>-, -Z<sup>105</sup>-N(R)-C(O)-N(R)-Z<sup>200</sup>-, R<sub>c</sub> and CH<sub>2</sub>OR<sub>c</sub>;
- where R<sub>c</sub> for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -CH<sub>2</sub>-NR<sub>d</sub>R<sub>e</sub>-, -W-(CH<sub>2</sub>)<sub>t</sub>-NR<sub>d</sub>R<sub>e</sub>-, -W-(CH<sub>2</sub>)<sub>t</sub>-O-alkyl, -W-(CH<sub>2</sub>)<sub>t</sub>-S-alkyl, or -W-(CH<sub>2</sub>)<sub>t</sub>-OH;
- Z<sup>105</sup> for each occurrence is independently a covalent bond or (C<sub>1</sub>-C<sub>6</sub>);
- Z<sup>200</sup> for each occurrence is independently a substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>), substituted or unsubstituted phenyl or substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-phenyl;
- R<sub>d</sub> and R<sub>e</sub> for each occurrence are independently H, alkyl, alkanoyl or SO<sub>2</sub>-alkyl; or R<sub>d</sub>, R<sub>e</sub> and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;
- t for each occurrence is independently an integer from 2 to 6;
- W for each occurrence is independently a direct bond or O, S, S(O), S(O)<sub>2</sub>, or NR<sub>f</sub>, wherein R<sub>f</sub> for each occurrence is independently H or alkyl; or
- R<sub>1</sub> is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;
- R<sub>3</sub> for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted -C(O)-heteroaryl or substituted or unsubstituted alkoxy;
- A is -(C<sub>1</sub>-C<sub>6</sub>)-, -O-, -S-, -S(O)<sub>p</sub>-, -N(R)-, -N(C(O)OR)-, -N(C(O)R)-, -N(SO<sub>2</sub>R)-, -CH<sub>2</sub>O-, -CH<sub>2</sub>S-, -CH<sub>2</sub>N(R)-, -CH(NR)-, -CH<sub>2</sub>N(C(O)R)-, -CH<sub>2</sub>N(C(O)OR)-, -CH<sub>2</sub>N(SO<sub>2</sub>R)-, -CH(NHR)-, -CH(NHC(O)R)-, -CH(NHSO<sub>2</sub>R)-, -CH(NHC(O)OR)-, -CH(OC(O)R)-, -

$\text{CH}(\text{OC}(\text{O})\text{NHR})-$ ;  $-\text{CH}=\text{CH}-$ ;  $-\text{C}(=\text{NOR})-$ ;  $-\text{C}(\text{O})-$ ;  $-\text{CH}(\text{OR})-$ ;  $-\text{C}(\text{O})\text{N}(\text{R})-$ ;  $-\text{N}(\text{R})\text{C}(\text{O})-$ ;  $-\text{N}(\text{R})\text{S}(\text{O})_p-$ ;  $-\text{OC}(\text{O})\text{N}(\text{R})-$ ;  $-\text{N}(\text{R})-\text{C}(\text{O})-(\text{CH}_2)_n-\text{N}(\text{R})-$ ;  $-\text{N}(\text{R})\text{C}(\text{O})\text{O}-$ ;  $-\text{N}(\text{R})-(\text{CH}_2)_{n+1}-\text{C}(\text{O})-$ ;  $-\text{S}(\text{O})_p\text{N}(\text{R})-$ ;  $-\text{O}-(\text{CR}_2)_{n+1}-\text{C}(\text{O})-$ ;  $-\text{O}-(\text{CR}_2)_{n+1}-\text{O}-$ ;  $-\text{N}(\text{C}(\text{O})\text{R})\text{S}(\text{O})_p-$ ;  $-\text{N}(\text{R})\text{S}(\text{O})_p\text{N}(\text{R})-$ ;  $-\text{N}(\text{R})-\text{C}(\text{O})-(\text{CH}_2)_n-\text{O}-$ ;  $-\text{C}(\text{O})\text{N}(\text{R})\text{C}(\text{O})-$ ;  $-\text{S}(\text{O})_p\text{N}(\text{R})\text{C}(\text{O})-$ ;  $-\text{OS}(\text{O})_p\text{N}(\text{R})-$ ;  $-\text{N}(\text{R})\text{S}(\text{O})_p\text{O}-$ ;  $-\text{N}(\text{R})\text{S}(\text{O})_p\text{C}(\text{O})-$ ;  $-\text{SO}_p\text{N}(\text{C}(\text{O})\text{R})-$ ;  $-\text{N}(\text{R})\text{SO}_p\text{N}(\text{R})-$ ;  $-\text{C}(\text{O})\text{O}-$ ;  $-\text{N}(\text{R})\text{P}(\text{OR}_b)\text{O}-$ ;  $-\text{N}(\text{R})\text{P}(\text{OR}_b)-$ ;  $-\text{N}(\text{R})\text{P}(\text{O})(\text{OR}_b)-$ ;  $-\text{N}(\text{C}(\text{O})\text{R})\text{P}(\text{OR}_b)\text{O}-$ ;  $-\text{N}(\text{C}(\text{O})\text{R})\text{P}(\text{OR}_b)-$ ;  $-\text{N}(\text{C}(\text{O})\text{R})\text{P}(\text{O})(\text{OR}_b)\text{O}-$ , or  $-\text{N}(\text{C}(\text{O})\text{R})\text{P}(\text{OR}_b)-$ ;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R<sub>b</sub> for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R<sub>b</sub> together form a five- or six-membered heterocyclic ring; or

A is NRSO<sub>2</sub> and R, R<sub>a</sub> and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1; or

Z<sup>110</sup>-A-Z<sup>111</sup> taken together is a covalent bond; and

R<sub>2</sub> is H or a group of the formula -Z<sup>101</sup>-Z<sup>102</sup>,

Z<sup>101</sup> is a covalent bond,  $-(\text{C}_1-\text{C}_6)-$ ,  $-(\text{C}_1-\text{C}_6)-\text{O}-$ ,  $-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})-$ ,  $-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})\text{O}-$ ,  $-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})-\text{NH}-$ ,  $-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})-\text{N}((\text{C}_1-\text{C}_6))-$  or a substituted or unsubstituted phenyl group;

Z<sup>102</sup> is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more

- substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted
- 5 -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, substituted or unsubstituted -N((C<sub>1</sub>-C<sub>6</sub>)-OR)<sub>2</sub>, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-C(O)<sub>2</sub>R, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-C(O)N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or
- 10 unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected
- 15 from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N(R)<sub>2</sub>, substituted or
- 20 unsubstituted -C(O)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or
- R<sub>2</sub> is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or
- 25 unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene,
- 30 substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylencarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a

- substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted
- 5 azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted aryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted alkyl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted heteroaryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted aryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted alkyl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted
- 10 or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted
- 15 heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;
- 20 a is 1 and D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are CR<sub>a</sub>; or
- a is 0, and one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is NR<sub>a</sub>, one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is CR<sub>a</sub> and the remainder are independently selected from the group
- 25 consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above;
- b is 1 and D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are CR<sub>a</sub>; or
- b is 0, and one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is NR<sub>a</sub>, one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is CR<sub>a</sub> and the remainder are independently selected from the group
- 30 consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above; and
- n for each occurrence is independently an integer from 0 to 6; provided that when A is -N(R)-, Z<sup>110</sup> and Z<sup>111</sup> are each a covalent bond, and



- $R_2$  is a 3,4-dihydroxytetrahydrofuran-2-yl or a 3,4-diacyloxytetrahydrofuran-2-yl, then  $Z^{100}$  is not alkyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl or pyrrolidinyl;
- provided that when  $Z^{110}$  and  $Z^{111}$  are each a covalent bond, and  $R_2$  is a 3,4-dihydroxytetrahydrofuran-2-yl or a 3,4-diacyloxytetrahydrofuran-2-yl,  $Z^{100}$  is a substituted or unsubstituted alkyl, then A is not alkyl, -O-, -C(O)-, -NHC(O)- or -C(O)O-;
- provided that when  $Z^{110}$ -A- $Z^{111}$  taken together are a covalent bond, then  $Z^{100}$  is not alkyl;
- provided that when  $Z^{110}$ -A- $Z^{111}$  taken together are a  $C_1$ - $C_6$  alkyl, then  $Z^{100}$  is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl; and
- provided that when  $R_2$  is a substituted or unsubstituted cyclopentyl,  $Z^{100}$  is an substituted or unsubstituted alkyl,  $Z^{110}$  and  $Z^{111}$  are each a covalent bond, then A is not -O-, -C(O)O-, or -N(R)-.
2. The compound of Claim 1 wherein  $R_3$  is H;  $R_1$  for each occurrence is independently selected from the group consisting of F, Cl, Br, I,  $CH_3$ ,  $NO_2$ ,  $OCF_3$ ,  $OCH_3$ , CN,  $CO_2CH_3$ ,  $CF_3$ ,  $-CH_2NR_4R_6$ , t-butyl, pyridyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzenesulfonyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenyl, substituted or unsubstituted amino, carboxyl, substituted or unsubstituted tetrazolyl, and substituted or unsubstituted styryl.
3. The compound of Claim 1 wherein  $R_3$  is H;  $R_4$  for each occurrence is independently selected from the group consisting of F, Cl, Br, I,  $CH_3$ ,  $NO_2$ ,  $OCF_3$ ,  $OCH_3$ , CN,  $CO_2CH_3$ ,  $CF_3$ , t-butyl, pyridyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzenesulfonyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenyl, substituted or unsubstituted amino, carboxyl, substituted or unsubstituted tetrazolyl, and substituted or unsubstituted styryl.

4. The compound of Claim 1 wherein  $R_3$  is H;  $R_2$  is of the formula



- 5 wherein n is 1, 2 or 3.

5. The compound of Claim 1 wherein  $R_3$  is H;  $R_2$  is of the formula



wherein:

- 10 m is 0, 1, 2 or 3;

$R_8$  is H or  $-(CH_2)_pN(R_4)R_5$ ;

p is an integer from 2 to 6;

$R_4$  and  $R_5$  are each, independently, H, azabicycloalkyl or Y-Z;

Y is selected from the group consisting of  $-C(O)-$ ,  $-(CH_2)_q-$ ,  $-S(O)_2-$ ,  $-C(O)O-$

- 15 ,  $-SO_2NH-$ ,  $-CONH-$ ,  $-(CH_2)_qO-$ ,  $-(CH_2)_qNH-$ , and  $-(CH_2)_qS(O)_r-$ ;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is a substituted or unsubstituted moiety selected from the group consisting

of alkyl, alkoxy, amino, aryl, heteroaryl and heterocycloalkyl group;

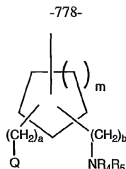
- 20 or

$R_4$ ,  $R_5$  and the nitrogen atom to which they are attached together form a 3, 4,

5, 6 or 7-membered, substituted or unsubstituted heterocyclic or

heterobicyclic group.

- 25 6. The compound of Claim 1 wherein  $R_3$  is H;  $R_2$  is of the formula



wherein:

m is 0, 1, 2 or 3;

5 a and b are each, independently, an integer from 0 to 6;

Q is -OR<sub>6</sub> or -NR<sub>4</sub>R<sub>5</sub>;

each R<sub>4</sub> and R<sub>5</sub> is, independently, H, azabicycloalkyl or Y-Z;

Y is selected from the group consisting of -C(O)-, -(CH<sub>2</sub>)<sub>q</sub>-, -S(O)<sub>2</sub>-, -C(O)O-  
 , -SO<sub>2</sub>NH-, -CONH-, (CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, and -(CH<sub>2</sub>)<sub>q</sub>S(O)<sub>r</sub>-;

10 q is an integer from 0 to 6;

r is 0, 1 or 2; and

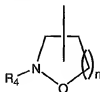
Z is a substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy,  
 amino, aryl, heteroaryl or heterocycloalkyl group; or

R<sub>4</sub>, R<sub>5</sub> and the nitrogen atom to which they are attached together form a 3, 4,

15 5, 6 or 7-membered, substituted or unsubstituted heterocyclic or  
 heterobicyclic group; and

R<sub>6</sub> is hydrogen or a substituted or unsubstituted alkyl group.

7. The compound of Claim 1 wherein R<sub>3</sub> is H; R<sub>2</sub> is of the formula



20

wherein:

n is 1, 2 or 3;

R<sub>4</sub> is H, azabicycloalkyl or Y-Z;

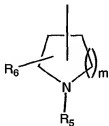
Y is selected from the group consisting of -C(O)-, -(CH<sub>2</sub>)<sub>q</sub>-, -S(O)<sub>2</sub>-, -C(O)O-  
 25 , -SO<sub>2</sub>NH-, -CONH-, (CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, and -(CH<sub>2</sub>)<sub>q</sub>S(O)<sub>r</sub>-;

q is an integer 0 to 6;

r is 0, 1 or 2; and

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted amino, aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group.

8. The compound of Claim 1 wherein R<sub>3</sub> is H; R<sub>2</sub> is of the formula



wherein;

m is 0, 1, 2 or 3;

R<sub>5</sub> is H, azabicycloalkyl or Y-Z;

Y is selected from the group consisting of a covalent bond, -C(O)-, -(CH<sub>2</sub>)<sub>q</sub>-, -S(O)<sub>2</sub>-, -C(O)O-, -SO<sub>2</sub>NH-, -CONH-, -(CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, -(CH<sub>2</sub>)<sub>q</sub>C(O)-, -C(O)(CH<sub>2</sub>)<sub>q</sub>- and -(CH<sub>2</sub>)<sub>q</sub>S(O)-, where the alkyl portion of -(CH<sub>2</sub>)<sub>q</sub>-, -(CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, -(CH<sub>2</sub>)<sub>q</sub>C(O)-, -C(O)(CH<sub>2</sub>)<sub>q</sub>- and -(CH<sub>2</sub>)<sub>q</sub>S(O)- is optionally substituted by a halogen, hydroxy or an alkyl group;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

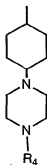
Y and Z together are a natural or unnatural amino acid, which may be mono- or di-alkylated at the amine nitrogen; and

R<sub>6</sub> represents one or more substituents each independently selected from the group consisting of hydrogen, hydroxy, oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted

-780-

alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heterocyclylcarbonyl, substituted or unsubstituted aminoalkyl and substituted or unsubstituted arylalkyl;  
 provided that the carbon atoms adjacent to the nitrogen atom are not substituted by a hydroxy group.

9. The compound of Claim 1 wherein  $R_3$  is H;  $R_2$  is of the formula



wherein:

$R_4$  is H, substituted or unsubstituted alkyl, substituted or unsubstituted azabicycloalkyl or Y-Z;

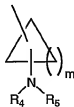
Y is selected from the group consisting of  $-C(O)-$ ,  $-(CH_2)_q-$ ,  $-S(O)_2-$ ,  $-C(O)O-$ ,  $-SO_2NH-$ ,  $-CONH-$ ,  $-(CH_2)_qO-$ ,  $-(CH_2)_qNH-$ , and  $-(CH_2)_qS(O)_r-$ ;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl.

10. The compound of Claim 1 wherein  $R_3$  is H;  $R_2$  is of the formula



wherein:

m is an integer from 1 to 6;

R<sub>4</sub> and R<sub>5</sub> are each, independently, H, substituted or unsubstituted azabicycloalkyl or Y-Z;

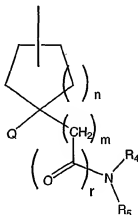
Y is selected from the group consisting of -C(O)-, -(CH<sub>2</sub>)<sub>q</sub>-, -S(O)<sub>2</sub>-, -C(O)O-,  
5 , -SO<sub>2</sub>NH-, -CONH-, -(CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, and -(CH<sub>2</sub>)<sub>q</sub>S(O)<sub>r</sub>-;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted amino,  
substituted or unsubstituted aryl, substituted or unsubstituted  
10 heteroaryl or substituted or unsubstituted heterocycloalkyl group; or  
R<sub>4</sub>, R<sub>5</sub> and the nitrogen atom to which they are attached together form a 3, 4,  
5, 6 or 7-membered, substituted or unsubstituted heterocyclic or  
substituted or unsubstituted heterobicyclic group.

15 11. The compound of Claim 1 wherein R<sub>3</sub> is H; R<sub>2</sub> is of the formula



wherein

n is an integer from 0 to 4;

r is 0 and m is an integer from 1 to 6; or

20 r is 1 and m is an integer from 0 to 6;

Q is -OR<sub>6</sub> or -NR<sub>4</sub>R<sub>5</sub>;

each R<sub>4</sub> and R<sub>5</sub> is, independently, H, substituted or unsubstituted  
azabicycloalkyl or Y-Z;

Y is selected from the group consisting of -C(O)-, -(CH<sub>2</sub>)<sub>q</sub>-, -S(O)<sub>2</sub>-, -C(O)O-  
25 , -SO<sub>2</sub>NH-, -CONH-, -(CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, and -(CH<sub>2</sub>)<sub>q</sub>S(O)<sub>r</sub>-;

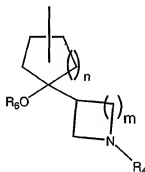
q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy,  
substituted or unsubstituted amino, substituted or unsubstituted aryl,  
substituted or unsubstituted heteroaryl or substituted or unsubstituted  
heterocycloalkyl group; or

R<sub>4</sub>, R<sub>5</sub> and the nitrogen atom to which they are attached together form a 3, 4,  
5 or 6-membered, substituted or unsubstituted heterocyclic group; and  
R<sub>6</sub> is hydrogen or a substituted or unsubstituted alkyl group.

12. The compound of Claim 1 wherein R<sub>3</sub> is H; R<sub>2</sub> is of the formula



wherein:

n is an integer from 0 to 4;

m is an integer from 0 to 6;

R<sub>4</sub> is H, substituted or unsubstituted azabicycloalkyl or Y-Z;

Y is selected from the group consisting of -C(O)-, -(CH<sub>2</sub>)<sub>q</sub>-, -S(O)<sub>2</sub>-, -C(O)O-  
, -SO<sub>2</sub>NH-, -CONH-, -(CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, and -(CH<sub>2</sub>)<sub>q</sub>S(O)<sub>r</sub>-;

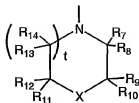
q is an integer from 0 to 6;

r is 0, 1 or 2;

Z is substituted or unsubstituted alkyl, substituted or unsubstituted amino,  
substituted or unsubstituted aryl, substituted or unsubstituted  
heteroaryl or substituted or unsubstituted heterocycloalkyl; and  
R<sub>6</sub> is hydrogen or a substituted or unsubstituted alkyl group.

13. The compound of Claim 10 wherein R<sub>4</sub>, R<sub>5</sub> and the nitrogen atom together  
form a heterocyclic group of the formula

-783-



wherein:

R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub> and R<sub>14</sub> are each, independently, lower alkyl or hydrogen; or

at least one pair of substituents R<sub>7</sub> and R<sub>8</sub>; R<sub>9</sub> and R<sub>10</sub>; R<sub>11</sub> and R<sub>12</sub>; or R<sub>13</sub> and R<sub>14</sub> together are an oxygen atom; or

at least one of R<sub>7</sub> and R<sub>9</sub> is cyano, CONHR<sub>15</sub>, COOR<sub>15</sub>, CH<sub>2</sub>OR<sub>15</sub> or CH<sub>2</sub>NR<sub>15</sub>(R<sub>16</sub>), and

R<sub>15</sub> and R<sub>16</sub> are each, independently, H, azabicycloalkyl or V-L;

V is selected from the group consisting of -C(O)-, -(CH<sub>2</sub>)<sub>p</sub>-S(O)<sub>2</sub>-, -C(O)O-, -SO<sub>2</sub>NH-, -CONH-, (CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, and -(CH<sub>2</sub>)<sub>q</sub>S(O)<sub>r</sub>-;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2;

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl; or R<sub>15</sub>, R<sub>16</sub> and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocyclic or a substituted or unsubstituted heterobicyclic group;

X is O, S, SO, SO<sub>2</sub>, CH<sub>2</sub>, CHOR<sub>17</sub> or NR<sub>17</sub>;

R<sub>17</sub> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, -C(NH)NH<sub>2</sub>, -C(O)R<sub>17</sub>, or -C(O)OR<sub>18</sub>;

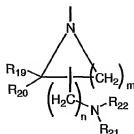
R<sub>18</sub> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl; and t is 0 or 1.

14. The compound of Claim 10 wherein R<sub>4</sub>, R<sub>5</sub> and the nitrogen atom together



-784-

form a heterocycle of the formula



wherein:

R<sub>19</sub> and R<sub>20</sub> are each, independently, hydrogen or lower alkyl; or R<sub>19</sub> and R<sub>20</sub> together are an oxygen atom;

R<sub>21</sub> and R<sub>22</sub> are each, independently, H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of -C(O)-, -(CH<sub>2</sub>)<sub>p-r</sub>-S(O)<sub>2</sub>-, -C(O)O-, -SO<sub>2</sub>NH-, -CONH-, (CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, and -(CH<sub>2</sub>)<sub>q</sub>S(O)<sub>r</sub>-;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted

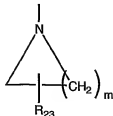
heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

R<sub>21</sub>, R<sub>22</sub> and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocyclic group; and

m is an integer from 1 to 6; and

n is an integer from 0 to 6.

15. The compound of Claim 10 wherein R<sub>4</sub>, R<sub>5</sub> and the nitrogen atom together form a heterocyclic group of the formula



wherein:

m is an integer from 1 to 6;

$R_{23}$  is  $CH_2OH$ ,  $NRR'$ ,  $C(O)NRR'$  or  $COOR$ ; and

$R$  and  $R'$  are each, independently, hydrogen or substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl.

5

16. The compound of Claim 10 wherein  $R_4$ ,  $R_5$  and the nitrogen atom together form a heterocyclic group of the formula



10

wherein:

$R_{24}$  is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, carboxyl, cyano,  $C(O)OR_{25}$ ,  $CH_2OR_{25}$ ,  $CH_2NR_{26}R_{27}$  or  $C(O)NHR_{26}$ ;

15

$R_{25}$  is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclic or substituted or unsubstituted heterocycloaryl; and

$R_{26}$  and  $R_{27}$  are each, independently, H, substituted or unsubstituted azabicycloalkyl or V-L;

20

V is selected from the group consisting of  $-C(O)-$ ,  $-(CH_2)_p-S(O)_2-$ ,  $-C(O)O-$ ,  $-SO_2NH-$ ,  $-CONH-$ ,  $(CH_2)_qO-$ ,  $-(CH_2)_qNH-$ , and  $-(CH_2)_qS(O)_r-$ ;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

25

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl; or  $R_{26}$ ,  $R_{27}$  and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocyclic group.

- 30 17. The compound of Claim 10 wherein at least one of  $R_4$  and  $R_5$  is of the

-786-

formula Y-Z, wherein Z is of the formula



wherein:

T is C(O), S, SO, SO<sub>2</sub>, CHOR or NR;

- 5 R is hydrogen or a substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl group; and  
n is 0, 1 or 2.

18. The compound of Claim 10 wherein:

10 at least one of R<sub>4</sub> and R<sub>5</sub> is of the formula Y-Z;

Z is of the formula -N(R<sub>28</sub>)R<sub>29</sub>; and

R<sub>28</sub> and R<sub>29</sub> are each, independently, substituted or unsubstituted

carboxyalkyl, substituted or unsubstituted alkoxyacetylalkyl,

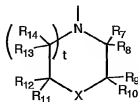
substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted

15 alkylsulfonyl, substituted or unsubstituted alkylcarbonyl or

substituted or unsubstituted cyanoalkyl; or

R<sub>28</sub> and R<sub>29</sub>, together with the nitrogen atom, form a five- or six-membered  
substituted or unsubstituted heterocyclic group.

19. The compound of Claim 11 wherein R<sub>4</sub>, R<sub>5</sub> and the nitrogen atom together  
form a heterocycle of the formula



wherein:

R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub> and R<sub>14</sub> are each, independently, lower alkyl or

hydrogen; or

at least one pair of substituents R<sub>7</sub> and R<sub>8</sub>; R<sub>9</sub> and R<sub>10</sub>; R<sub>11</sub> and R<sub>12</sub>; or R<sub>13</sub>

and R<sub>14</sub> together are an oxygen atom; or

at least one of R<sub>7</sub> and R<sub>9</sub> is cyano, CONHR<sub>15</sub>, COOR<sub>15</sub>, CH<sub>2</sub>OR<sub>15</sub> or

5 CH<sub>2</sub>NR<sub>15</sub>(R<sub>16</sub>); and

R<sub>15</sub> and R<sub>16</sub> are each, independently, H, substituted or unsubstituted

azabicycloalkyl or V-L;

V is selected from the group consisting of -C(O)-, -(CH<sub>2</sub>)<sub>p</sub>-, -S(O)<sub>2</sub>-, -C(O)O-,

-SO<sub>2</sub>NH-, -CONH-, (CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>NH-, and -(CH<sub>2</sub>)<sub>q</sub>S(O)<sub>r</sub>-;

10 p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino,

substituted or unsubstituted aryl, substituted or unsubstituted

15 heteroaryl or substituted or unsubstituted heterocycloalkyl; or

R<sub>15</sub>, R<sub>16</sub> and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered,

substituted or unsubstituted heterocyclic or heterobicyclic group; and

X is O, S, SO, SO<sub>2</sub>, CH<sub>2</sub>, CHOR<sub>17</sub> or NR<sub>17</sub>;

R<sub>17</sub> is hydrogen, substituted or unsubstituted alkyl, substituted or

20 unsubstituted aryl, substituted or unsubstituted arylalkyl, -C(NH)NH<sub>2</sub>,

-C(O)R<sub>18</sub>, or -C(O)OR<sub>18</sub>;

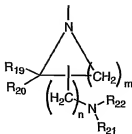
R<sub>18</sub> is hydrogen, substituted or unsubstituted alkyl, substituted or

unsubstituted aryl or substituted or unsubstituted arylalkyl; and

t is 0 or 1.

25

20. The compound of Claim 11 wherein R<sub>4</sub>, R<sub>5</sub> and the nitrogen atom together form a heterocycle of the formula



wherein:

$R_{19}$  and  $R_{20}$  are each, independently, hydrogen or lower alkyl; or

$R_{19}$  and  $R_{20}$  together are an oxygen atom; and

$R_{21}$  and  $R_{22}$  are each, independently, H, substituted or unsubstituted

5 azabicycloalkyl or V-L;

V is selected from the group consisting of  $-C(O)-$ ,  $-(CH_2)_p-$ ,  $-S(O)_2-$ ,  $-C(O)O-$ ,  
 $-SO_2NH-$ ,  $-CONH-$ ,  $(CH_2)_qO-$ ,  $-(CH_2)_qNH-$ , and  $-(CH_2)_qS(O)_r-$ ;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

10 r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino,  
 substituted or unsubstituted aryl, substituted or unsubstituted  
 heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

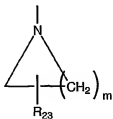
$R_{21}$ ,  $R_{22}$  and the nitrogen atom together form a 3, 4, 5 or 6-membered,

15 substituted or unsubstituted heterocyclic group; and

m is an integer from 1 to 6; and

n is an integer from 0 to 6.

21. The compound of Claim 11 wherein  $R_4$ ,  $R_5$  and the nitrogen atom together  
 20 form a heterocyclic group of the formula



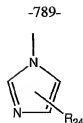
wherein:

m is an integer from 1 to 6; and

$R_{23}$  is  $CH_2OH$ ,  $NRR'$ ,  $C(O)NRR'$  or  $COOR$ ;

25 R is hydrogen or a substituted or unsubstituted alkyl, substituted or  
 unsubstituted aryl or substituted or unsubstituted arylalkyl group.

22. The compound of Claim 11 wherein  $R_4$ ,  $R_5$  and the nitrogen atom together  
 form a heterocyclic group of the formula



wherein:

$R_{24}$  is substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl, carboxyl, cyano,  $C(O)OR_{25}$ ,  $CH_2OR_{25}$ ,  $CH_2NR_{26}R_{27}$  or  $C(O)NHR_{26}$ ;

$R_{25}$  is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclic or substituted or unsubstituted heterocycloaryl group;

$R_{26}$  and  $R_{27}$  are each, independently, H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of  $-C(O)-$ ,  $-(CH_2)_p-$ ,  $-S(O)_2-$ ,  $-C(O)O-$ ,  $-SO_2NH-$ ,  $-CONH-$ ,  $(CH_2)_qO-$ ,  $-(CH_2)_qNH-$ , and  $-(CH_2)_qS(O)_r-$ ;

p is an integer from 0 to 6;

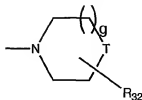
q is an integer from 0 to 6;

r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

$R_{26}$ ,  $R_{27}$  and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocyclic group.

23. The compound of Claim 11 wherein at least one of  $R_4$  and  $R_5$  is of the formula Y-Z, wherein Z is of the formula



wherein:

g is 0 or 1;

T is  $C(O)$ , O, S, SO,  $SO_2$ ,  $CH_2$ ,  $CHOR_{17}$  or  $NR_{17}$ ;

$R_{17}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl,  $-C(NH)NH_2$ ,  $-C(O)R_{18}$ , or  $-C(O)OR_{18}$ ;

$R_{18}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl; and

$R_{32}$  is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl.

24. The compound of Claim 11 wherein;  
at least one of  $R_4$  and  $R_5$  is of the formula Y-Z;

Z is of the formula  $-N(R_{28})R_{29}$ ; and

$R_{28}$  and  $R_{29}$  are each, independently, substituted or unsubstituted carboxyalkyl, substituted or unsubstituted alkoxy carbonylalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted cyanoalkyl; or

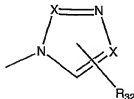
$R_{28}$  and  $R_{29}$ , together with the nitrogen atom, form a five- or six-membered substituted or unsubstituted heterocyclic group.

25. The compound of Claim 8 wherein:

$R_5$  is Y-Z, wherein Z is of the formula  $N(R_{30})R_{31}$ ; and

$R_{30}$  and  $R_{31}$  are each, independently, hydrogen, alkyl, alkoxy carbonyl, alkoxyalkyl, hydroxyalkyl, aminocarbonyl, cyano, alkylcarbonyl or arylalkyl.

26. The compound of Claim 8 wherein  $R_5$  is Y-Z, wherein Z is of the formula

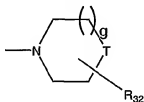


wherein:

each X is, independently, CH or N; and

R<sub>32</sub> is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl group.

27. The compound of Claim 8 wherein R<sub>5</sub> is Y-Z, wherein Z is of the formula



wherein:

g is 0 or 1;

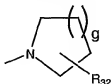
T is O, S, SO, SO<sub>2</sub>, CH<sub>2</sub>, CHOR<sub>17</sub> or NR<sub>17</sub>;

R<sub>17</sub> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, C(O)NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -C(O)R<sub>17</sub>, or -C(O)OR<sub>18</sub>;

R<sub>18</sub> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl; and

R<sub>32</sub> is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl group.

28. The compound of Claim 8 wherein R<sub>5</sub> is Y-Z, wherein Z is of the formula



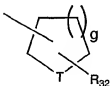


wherein:

g is 0, 1 or 2; and

R<sub>32</sub> is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted aryl carbonyl or substituted or unsubstituted arylalkyl group.

29. The compound of Claim 8 wherein R<sub>5</sub> is Y-Z, wherein Z is of the formula



wherein

T is C(O), O, S, SO, SO<sub>2</sub>, CH<sub>2</sub>, CHOR<sub>17</sub> or NR<sub>17</sub>;

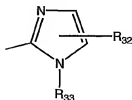
R<sub>17</sub> is hydrogen, substituted or unsubstituted alkyl, aryl, arylalkyl, -C(NH)NH<sub>2</sub>, -C(O)R<sub>18</sub>, or -C(O)OR<sub>18</sub>;

R<sub>18</sub> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl;

g is 0 or 1; and

R<sub>32</sub> is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted aryl carbonyl or substituted or unsubstituted arylalkyl group.

30. The compound of Claim 8 wherein R<sub>5</sub> is Y-Z, wherein Z is of the formula



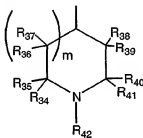
wherein:

R<sub>32</sub> is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or

unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, alkylcarbonyl, substituted or unsubstituted thioalkoxy or substituted or unsubstituted arylalkyl; and

$R_{33}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted aminocarbonyl, perhaloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl.

31. The compound of Claim 1 wherein  $R_3$  is H;  $R_2$  is of the formula



wherein:

$m$  is 0 or 1; and

$R_{34}$ ,  $R_{35}$ ,  $R_{36}$ ,  $R_{37}$ ,  $R_{38}$ ,  $R_{39}$ ,  $R_{40}$  and  $R_{41}$  are each, independently, methyl or hydrogen; or

at least one pair of substituents  $R_{34}$  and  $R_{35}$ ;  $R_{36}$  and  $R_{37}$ ;  $R_{38}$  and  $R_{39}$ ; or  $R_{40}$

and  $R_{41}$  together are an oxygen atom; and

$R_{42}$  is H, substituted or unsubstituted azabicycloalkyl or Y-Z;

Y is selected from the group consisting of  $-C(O)-$ ,  $-(CH_2)_p-S(O)_2-$ ,  $-C(O)O-$ ,  $-SO_2NH-$ ,  $-CONH-$ ,  $(CH_2)_qO-$ ,  $-(CH_2)_qNH-$ , and  $-(CH_2)_qS(O)_r-$ ;

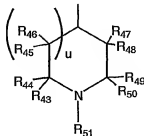
$p$  is an integer from 0 to 6;

$q$  is an integer from 0 to 6;

$r$  is 0, 1 or 2; and

Z is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl or substituted or unsubstituted heterocycloalkyl group; or  
 $R_{42}$  is of the formula



wherein:

5  $u$  is 0 or 1;

$R_{43}$ ,  $R_{44}$ ,  $R_{45}$ ,  $R_{46}$ ,  $R_{47}$ ,  $R_{48}$ ,  $R_{49}$  and  $R_{50}$  are each, independently, methyl or hydrogen; or

at least one pair of substituents  $R_{43}$  and  $R_{44}$ ;  $R_{45}$  and  $R_{46}$ ;  $R_{47}$  and  $R_{48}$ ; or  $R_{49}$  and  $R_{50}$  together are an oxygen atom; and

10  $R_{51}$  is H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of  $-C(O)-$ ,  $-(CH_2)_p-$ ,  $-S(O)_2-$ ,  $-C(O)O-$ ,  $-SO_2NH-$ ,  $-CONH-$ ,  $(CH_2)_qO-$ ,  $-(CH_2)_qNH-$ , and  $-(CH_2)_qS(O)_r-$ ;

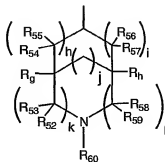
$p$  is an integer from 0 to 6;

$q$  is an integer from 0 to 6;

15  $r$  is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl.

20 32. The compound of Claim 1 wherein  $R_3$  is H;  $R_2$  is of the formula



wherein:

$h$ ,  $i$ ,  $j$ ,  $k$  and  $l$  are independently 0 or 1;

$R_{52}$ ,  $R_{53}$ ,  $R_{54}$ ,  $R_{55}$ ,  $R_{56}$ ,  $R_{57}$ ,  $R_{58}$ ,  $R_{59}$ ,  $R_g$  and  $R_h$  are each, independently,  
methyl or hydrogen; or

at least one pair of substituents  $R_{52}$  and  $R_{53}$ ;  $R_{54}$  and  $R_{55}$ ;  $R_{56}$  and  $R_{57}$ ; or  $R_{58}$   
and  $R_{59}$  together are an oxygen atom; and

$R_{60}$  is H, substituted or unsubstituted azabicycloalkyl or Y-Z;

Y is selected from the group consisting of  $-C(O)-$ ,  $-(CH_2)_p-$ ,  $-S(O)_2-$ ,  $-C(O)O-$ ,  
 $-SO_2NH-$ ,  $-CONH-$ ,  $-(CH_2)_qO-$ ,  $-(CH_2)_qNH-$ , and  $-(CH_2)_qS(O)_r-$ ;

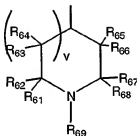
p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is substituted or unsubstituted alkyl, substituted or unsubstituted amino,  
substituted or unsubstituted aryl, substituted or unsubstituted  
heteroaryl or substituted or unsubstituted heterocycloalkyl; or

$R_{60}$  is of the formula



wherein:

v is 0 or 1;

$R_{61}$ ,  $R_{62}$ ,  $R_{63}$ ,  $R_{64}$ ,  $R_{65}$ ,  $R_{66}$ ,  $R_{67}$  and  $R_{68}$  are each, independently, lower alkyl  
or hydrogen; or

at least one pair of substituents  $R_{61}$  and  $R_{62}$ ;  $R_{63}$  and  $R_{64}$ ;  $R_{65}$  and  $R_{66}$ ; and  $R_{67}$   
and  $R_{68}$  together are an oxygen atom; and

$R_{69}$  is H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of  $-C(O)-$ ,  $-(CH_2)_p-$ ,  $-S(O)_2-$ ,  $-C(O)O-$ ,  
 $-SO_2NH-$ ,  $-CONH-$ ,  $(CH_2)_qO-$ ,  $-(CH_2)_qNH-$ , and  $-(CH_2)_qS(O)_r-$ ;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl.

33. A method of inhibiting one or more protein kinase activity in a patient  
5 comprising administering a therapeutically effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.
34. The method of Claim 33 wherein said protein kinase is selected from the  
10 group consisting of KDR, FGFR-1, PDGFR $\beta$ , PDGFR $\alpha$ , IGF-1R, c-Met, Flt-1, Flt-4, TIE-2, TIE-1, Lck, Src, fyn, Lyn, Blk, hck, fgr and yes.
35. A method of affecting hyperproliferative disorders in a patient comprising  
15 administering a therapeutically effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.
36. A method of affecting angiogenesis in a patient comprising administering a  
20 therapeutically effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.
37. The method of Claim 33 wherein the protein kinase is a protein  
25 serine/threonine kinase or a protein tyrosine kinase.
38. A method of treating one or more ulcers in a patient comprising  
administering a therapeutically effective amount of a compound of Claim 1  
or a physiologically acceptable salt, prodrug or biologically active  
30 metabolites thereof to said patient.
39. The method of Claim 38 wherein the ulcer or ulcers are caused by a bacterial  
or fungal infection; or the ulcer or ulcers are Mooren ulcers; or the ulcer or  
ulcers are a symptom of ulcerative colitis.

40. A method of treating a condition in a patient comprising administering a therapeutically effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient, wherein said condition is an ocular condition, a cardiovascular condition, a cancer, Crow-Fukase (POEMS) syndrome, a diabetic condition, sickle cell anaemia, chronic inflammation, systemic lupus, glomerulonephritis, synovitis, inflammatory bowel disease, Crohn's disease, glomerulonephritis, rheumatoid arthritis, osteoarthritis, multiple sclerosis, graft rejection, Lyme disease, sepsis, von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease, polycystic kidney disease, fibrosis, sarcoidosis, cirrhosis, thyroiditis, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma or edema following burns, trauma, radiation, stroke, hypoxia, ischemia, ovarian hyperstimulation syndrome, preeclampsia, menometrorrhagia, endometriosis, or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapoxvirus, protozoa or toxoplasmosis.
41. The method of Claim 40 wherein the ocular condition is ocular or macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser treatment complications, conjunctivitis, Stargardt's disease, Eales disease, retinopathy or macular degeneration.
42. The method of Claim 40 wherein the cardiovascular condition is atherosclerosis, restenosis, ischemia/reperfusion injury, vascular occlusion or carotid obstructive disease.
43. The method of Claim 40 wherein the cancer is a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy, Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma, leukemia or malignant ascites.

44. The method of Claim 40 wherein the diabetic condition is insulin-dependent diabetes mellitus glaucoma, diabetic retinopathy or microangiopathy.
- 5 45. A method of decreasing fertility in a patient, said method comprising the step of administering to the patient an effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolite thereof.
- 10 46. The method of Claim 36 wherein the compound or a physiologically acceptable salt, prodrug or biologically active metabolite thereof is administered in an amount effective to promote angiogenesis or vasculogenesis.
- 15 47. The method of Claim 34 wherein the protein kinase is Tie-2.
48. The method of Claim 46 wherein the compound of Formula I, or physiologically acceptable salt, prodrug or biologically active metabolite thereof, is administered in combination with a pro-angiogenic growth factor.
- 20 49. The method of Claim 48 wherein the pro-angiogenic growth factor is selected from the group consisting of VEGF, VEGF-B, VEGF-C, VEGF-D, VEGF-E, HGF, FGF-1, FGF-2, derivatives thereof and antiidiotypic antibodies.
- 25 50. The method of Claim 46 wherein the patient is suffering from anemia, ischemia, infarct, transplant rejection, a wound, gangrene or necrosis.
51. The method of Claim 33 wherein the protein kinase activity is involved in T cell activation, B cell activation, mast cell degranulation, monocyte activation, the potentiation of an inflammatory response or a combination thereof.
- 30

52. A compound according to Claim 1, wherein:

$R_3$  is H;

$R_2$  is  $-Z^{101}-Z^{102}$ ;

$Z^{101}$  is a covalent bond,  $-(C_1-C_6)-$ ,  $-(C_1-C_6)-O-$ ,  $-(C_1-C_6)-C(O)-$ ,  $-(C_1-$

5  $C_6)-C(O)O-$ ,  $-(C_1-C_6)-C(O)-NH-$ ,  $-(C_1-C_6)-C(O)-N((C_1-C_6))-$  or a substituted phenyl group; and

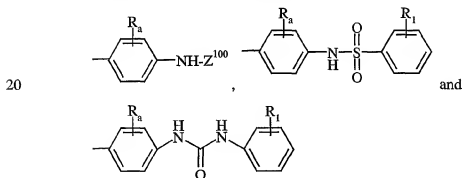
$Z^{102}$  is hydrogen, a substituted or unsubstituted alkyl group or a substituted or unsubstituted, saturated or unsaturated heterocyclic group.

10 53. A compound according to Claim 52, wherein:

$Z^{101}$  is selected from the group consisting of  $-CH_2-C(O)O-$ ,  $-CH_2-C(O)-$ ,  $-CH_2-C(O)-NH-$ ,  $-CH_2-C(O)-N(Me)-$ ,  $-CH(Me)-C(O)O-$ ,  $-(CH_2)_3-C(O)O-$ ,  $-CH(Me)-C(O)-NH-$  and  $-(CH_2)_3-C(O)-NH-$ ;

15  $Z^{102}$  is selected from the group consisting of hydrogen, methyl, ethyl, N,N-dimethylaminoethyl, N,N-diethylaminoethyl, 2-phenyl-2-hydroxyethyl, morpholino, piperazinyl, N-methylpiperazinyl and 2-hydroxymethylpyrrolidinyl.

54. A compound according to Claim 53, wherein G is selected from



wherein:

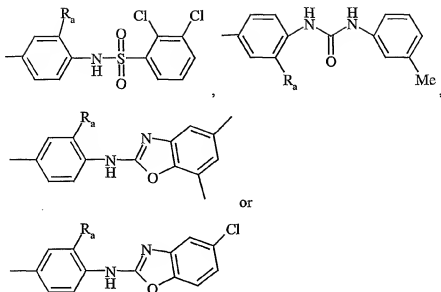
$Z^{100}$  is a substituted or unsubstituted benzoxazolyl or a substituted or unsubstituted benzthiazolyl.

25

55. A compound according to Claim 8, 9, 10 or 53, wherein G is



-800-

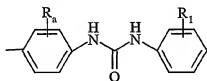


wherein there is only one  $R_a$  and it is H or F.

5

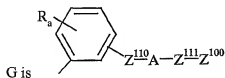
56. A compound according to Claim 52, wherein  $Z^{101}$  is a covalent bond; and  $Z^{102}$  is an optionally substituted pyridyl.

57. A compound according to Claim 56, wherein G is



10

58. A compound according to Claim 1, wherein  $R_3$  is H;  $R_2$  is cyclopentyl; and



G is

15

59. A compound according to Claim 58, wherein  $Z^{110}$  is hydrogen;  $A$  is O; and  $Z^{100}$  is optionally substituted phenyl, furanyl or thienyl, where  $Z^{100}$  is


optionally substituted with one or more substituents each independently selected from the group consisting of F, COOH, NO<sub>2</sub>, OMe, -COOMe, OCF<sub>3</sub> and CF<sub>3</sub>.

- 5 60. A compound according to Claim 58, wherein:  
 $Z^{110}$  is hydrogen;  
 A is -O-, -O-(CR<sub>2</sub>)<sub>n</sub>-C(O)- or -O-(CR<sub>2</sub>)<sub>n</sub>-O-;  
 n for each occurrence is 0 to 3;  
 $Z^{100}$  is an optionally substituted group selected from the group consisting of  
 10 cyclohexyl, phenyl, tetrahydropyranyl, tetrahydrofuranyl, isoxazolyl  
 and piperidinyl; where  $Z^{100}$  is optionally substituted with one or more  
 substituents selected from the group consisting of alkyl, alkoxy, halo,  
 hydroxy and alkoxycarbonyl.
- 15 61. A compound according to Claim 58, wherein R<sup>2</sup> is an optionally substituted  
 group selected from the group consisting of cyclobutyl and cyclohexyl.
62. A compound according to Claim 61, wherein R<sup>2</sup> is optionally substituted  
 with one or more substituents selected from the group consisting of hydroxy,  
 20 alkyl, hydroxyalkyl, carboxyalkyl and phenylalkoxyalkyl.
63. A compound according to Claim 62, wherein G is 4-phenoxyphenyl.
64. A compound according to Claim 6 wherein m is 2; a is 0; R<sub>6</sub> is H; b is 1 or 2;  
 25 and R<sub>4</sub> and R<sub>5</sub> are each hydrogen.
65. A compound according to Claim 8, wherein m is 0, 1 or 2;  
 R<sub>6</sub> is hydrogen; R<sub>5</sub> is H or Y-Z;  
 Y is a covalent bond, -C(O)-, -(CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>-, -(CH<sub>2</sub>)<sub>q</sub>C(O)- or -  
 30 C(O)(CH<sub>2</sub>)<sub>q</sub>-, where the alkyl portion of -(CH<sub>2</sub>)<sub>q</sub>O-, -(CH<sub>2</sub>)<sub>q</sub>-, -  
 (CH<sub>2</sub>)<sub>q</sub>C(O)- and -C(O)(CH<sub>2</sub>)<sub>q</sub>- is optionally substituted by a halogen,  
 hydroxy or an alkyl group; and

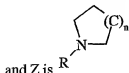
Z is hydrogen, alkyl, optionally substituted alkyl, alkoxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, or optionally substituted amino.

- 5 66. A compound according to Claim 65, wherein:

Z is hydrogen, methyl, ethyl, hydroxymethyl, methoxyethyl, N-methyl-  
piperidinyl, (t-butoxycarbonyl)(hydroxy)-piperidinyl,  
hydroxypiperidinyl, (hydroxymethyl)piperidinyl, (hydroxy)(methyl)-  
piperidinyl, morpholino, (methoxyethyl)piperizinyl,  
10 methylpiperizinyl, 4-piperidinylpiperidinyl, imidazolyl,  
methylimidazolyl, N-methylamino, N,N-dimethylamino, N-  
isopropylamino, N,N-diethylamino, 2,3-dihydroxypropylamino, 2-  
hydroxyethylamino, 3-hydroxypropylamino, methoxyethylamino,  
ethoxycarbonylmethylamino, phenylmethylamino, N-methyl-N-

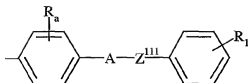
- 15 methoxyamino, , furanylmethylamino,  
piperidinylethylamino, N-(2-N,N-dimethylaminoethyl)-N-  
methylamino, 2-N,N-dimethylaminoethylamino, N-methyl-N-(N-  
methylpiperidin-4-yl)amino, 2-morpholino-ethylamino, 3-  
morpholino-propylamino, 3-imidazolylpropylamino, or 3-(2-  
20 oxopyrrolidinyl)propylamino.

67. A compound according to Claim 8, wherein m is 2; R<sub>5</sub> is Y-Z; Y is -C(O)-;



where n is 0, 1, 2 or 3.

- 25 68. A compound according to Claim 9, wherein  
R<sub>4</sub> is hydrogen or methyl;



G is ;

A is selected from the group consisting of O, -N(R)- and -N(R)C(O)-;

Z<sup>111</sup> is -(CH<sub>2</sub>)<sub>n</sub>-cycloalkyl-(CH<sub>2</sub>)<sub>n</sub>-;

R is hydrogen or alkyl;

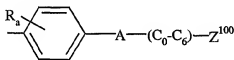
n is 0 to 5;

R<sub>a</sub> is one or more substituents each independently selected from the group consisting of H, OH, F, Cl, methyl and methoxy; and

R<sub>1</sub> is one or more substituents each independently selected from the group consisting of H, CN, F, CF<sub>3</sub>, OCF<sub>3</sub>, methyl, methoxy and an optionally substituted amino group; where said amino group is optionally substituted with one or two groups each independently selected from the group consisting of alkyl, alkoxyalkyl, phenyl, substituted phenyl, and optionally substituted heteroaryl.

69. A compound according to Claim 68, wherein R<sub>1</sub> is 4-methylphenylthio or 2-pyridinylthio.

70. A compound according to Claim 9, wherein

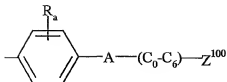


G is

where Z<sup>100</sup> is selected from the group consisting of benzo[b]thiophene, furanyl and thiophene.

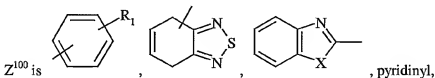
71. A compound according to Claim 9, wherein R<sub>a</sub> is alkoxy; A is -NH-C(O)-; and there is a covalent bond between A and Z<sup>100</sup>.

72. A compound according to Claims 1, 8 or 9, wherein



G is ;

A is selected from the group consisting of  $-\text{N}(\text{R})-\text{C}(\text{O})-\text{N}(\text{R})-$ ,  $-(\text{CH}_2)_n-$ ,  $\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})-$ ,  $-\text{N}(\text{R})-$  and  $-\text{N}(\text{R})-\text{SO}_2-$ ; R is hydrogen or alkyl;



5  $\text{Z}^{100}$  is thiazolyl, furanyl, benzofuranyl or oxazolyl;

X is S, O or  $\text{NR}^1$  where  $\text{R}^1$  for each occurrence is independently H or

Me;

$\text{R}_a$  is one or more substituents each independently selected from the group consisting of H and F; and

10  $\text{R}_1$  is one or more substituents each independently selected from the group consisting of H, F, Cl, Br,  $\text{NO}_2$ ,  $\text{CF}_3$ , alkyl, alkoxy and alkoxycarbonyl.

73. A compound according to Claim 72, wherein:

15  $\text{R}_4$  is methyl;

m is 1, 2 or 3;

$\text{R}_5$  is Y-Z;

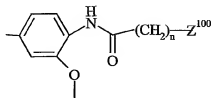
Y is  $-\text{C}(\text{O})\text{O}-$ ,  $-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})-(\text{CH}_2)_p-$ ; and

Z is aminoalkyl, N-alkylamino, N,N-dialkylamino or

20 hydroxyalkylaminoalkyl.

74. A compound according to Claim 9, wherein

$\text{R}_4$  is methyl;



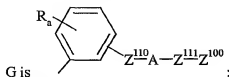
G is ; wherein

n is 0 to 3; and

$Z^{100}$  is an optionally substituted group selected from the group consisting of indolyl, indenyl, methyindenyl, methylindolyl, dimethylaminophenyl, phenyl, cyclohexyl and benzofuranyl.

5

75. A compound according to claim 9, wherein:



$Z^{100}$  is an optionally substituted group selected from the group consisting of phenyl, imidazolyl, indolyl, furanyl, benzofuranyl and 2,3-dihydrobenzofuranyl; where  $Z^{100}$  is optionally substituted with one or more substituents each independently selected from the group consisting of F, Cl, CN, optionally substituted alkyl, -O-(optionally substituted alkyl), -COOH,  $-Z^{105}-C(O)N(R)_2$ ,  $-Z^{105}-N(R)-C(O)-Z^{200}$ ,  $-Z^{105}-N(R)-S(O)_2-Z^{200}$ , and  $-Z^{105}-N(R)-C(O)-N(R)-Z^{200}$ ;

10

15  $Z^{105}$  is a covalent bond or  $(C_1-C_6)$ ;

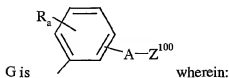
$Z^{200}$  is an optionally substituted group selected from group consisting of  $(C_1-C_6)$ , phenyl and  $-(C_1-C_6)$ -phenyl;

$Z^{110}$  and  $Z^{111}$  are each independently a covalent bond or  $(C_1-C_3)$  group optionally substituted with alkyl, hydroxy, COOH, CN or phenyl; and  
20 A is O,  $-N(R)-C(O)-N(R)-$ ,  $-N(R)-C(O)-O-$ ,  $-N(R)-$  or  $-N(R)-C(O)-$ , where R is H or alkyl.

20

76. A compound according to Claim 75, wherein  $R_4$  is methyl.

25 77. A compound according to Claim 8, 9 or 10, wherein



$Z^{100}$  is an optionally substituted group selected from the group consisting of benzoxazolyl, benzothiazolyl and benzimidazolyl.

78. A compound according to Claim 77, wherein;

$R_4$  is methyl;

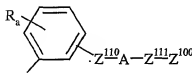
A is -NH-;

5 there is only one  $R_a$  and it is H or F; and

$Z^{100}$  is optionally substituted with one or more substituents each

independently selected from the group consisting of alkyl, halo,  $CF_3$ ,  
and alkoxy.

10 79. A compound according to Claim 9, wherein:



G is

$Z^{100}$  is an optionally substituted group selected from the group consisting of  
phenyl, pyrrolyl, pyridyl, benzimidazolyl, naphthyl and



; where  $Z^{100}$  is optionally substituted with one or

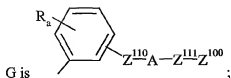
15 more substituents each independently selected from the group  
consisting of F, Cl, Br,  $NO_2$ , amino, N-alkylamino, N,N-  
dialkylamino, CN, optionally substituted alkyl, -O-(optionally  
substituted alkyl) and phenyl;

$Z^{110}$  and  $Z^{111}$  for each occurrence is independently ( $C_0$ - $C_3$ ) optionally  
20 substituted with optionally substituted phenyl; and

A is -N(R)-C(O)-N(R)-, -N(R)-S(O)<sub>2</sub>-, -N(R)-C(O)-, -N(R)- or -N(R)-C(O)-  
O-.

80. A compound according to Claim 79, wherein  $R_4$  is methyl and there is only  
25 one  $R_a$  and it is F.

81. A compound according to Claim 9 or 66, wherein



$\text{Z}^{100}$  is an optionally substituted group selected from the group consisting of phenyl, isoxazolyl, tetrahydronaphthyl, furanyl, benzofuranyl, pyridyl and indolyl; where  $\text{Z}^{100}$  is optionally substituted with one or more substituents each independently selected from the group consisting of F, CN,  $\text{NO}_2$ ,  $-\text{C}(\text{O})\text{H}$ ,  $-\text{CONH}_2$ ,  $-\text{NHSO}_2\text{CF}_3$ , optionally substituted alkyl, optionally substituted heteroaryl and  $-\text{O}$ -(optionally substituted alkyl);

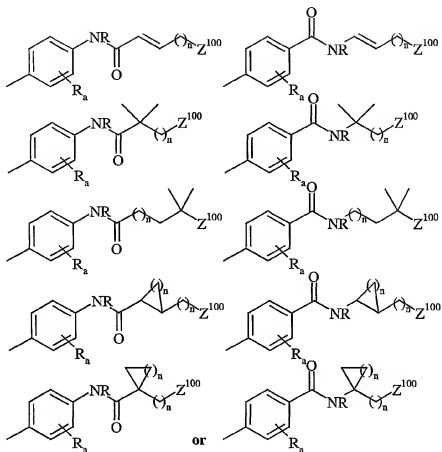
$\text{Z}^{110}$  and  $\text{Z}^{111}$  are each independently optionally substituted ( $\text{C}_0\text{-C}_3$ ); and

A is O,  $-\text{N}(\text{R})-\text{C}(\text{O})-(\text{CH}_2)_n-\text{N}(\text{R})-$ ,  $-\text{C}(\text{O})-\text{N}(\text{R})-$ ,  $-\text{N}(\text{R})-\text{C}(\text{O})-\text{O}-$ ,  $-\text{N}(\text{R})-\text{C}(\text{O})-$  or  $-\text{N}(\text{R})-$ .

82. A compound according to Claim 81, wherein  $\text{R}_4$  is methyl;  $\text{R}_4$  is H or methoxy; and  $\text{Z}^{110}$  and  $\text{Z}^{111}$  are each unsubstituted.

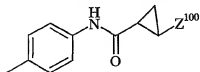
83. A compound according to Claim 9, wherein G is





where R is H or lower alkyl and n is for each occurrence is independently 1 to 6.

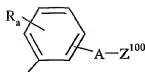
- 5 84. A compound according to Claim 83, wherein G is



85. A compound according to Claim 84, wherein  $Z^{100}$  is substituted or unsubstituted phenyl.

10

86. A compound according to Claim 8, 9 or 10, wherein

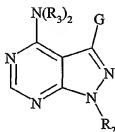


G is where  $Z^{100}$  is an optionally substituted group selected from the group consisting of benzoxazolyl, benzothiazolyl and benzimidazolyl.

- 5 87. A compound according to Claim 11 wherein n is 2;  $R_6$  is H; m is 1; r is 1; and  $R_4$  and  $R_5$  are each hydrogen.

88. A compound according to claim 64 or 87 wherein G is 4-phenoxyphenyl.

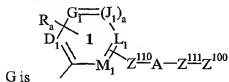
- 10 89. A compound of Formula (I)



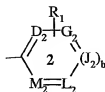
(I)

15

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:



G is

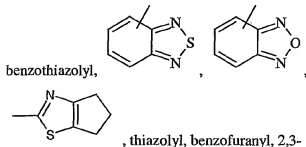


20

where  $Z^{100}$  is or a group optionally substituted with  $R_1$  selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl,

-810-

quinolinyl, quinoxaliny, quinazoliny, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,



dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuran, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

15       $Z^{110}$  is a covalent bond, or an optionally substituted ( $C_1-C_6$ ) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

20       $Z^{111}$  is a covalent bond, an optionally substituted ( $C_1-C_6$ ) or an optionally substituted  $-(CH_2)_n$ -cycloalkyl- $(CH_2)_n$ -; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

25       $R_q$  and  $R_1$  each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN,  $-NO_2$ ,  $-C(O)OH$ ,  $-C(O)H$ ,  $-OH$ ,  $-C(O)O$ -alkyl,  $-C(O)O$ -aryl,  $-C(O)O$ -heteroaryl,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted

- cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-S(O)<sub>p</sub>, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-S(O)<sub>p</sub>, substituted or unsubstituted heteroaryl-S(O)<sub>p</sub>, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z<sup>105</sup>-C(O)N(R)<sub>2</sub>, -Z<sup>105</sup>-N(R)-C(O)-Z<sup>200</sup>, -Z<sup>105</sup>-N(R)-S(O)<sub>2</sub>-Z<sup>200</sup>, -Z<sup>105</sup>-N(R)-C(O)-N(R)-Z<sup>200</sup>, R<sub>e</sub> and CH<sub>2</sub>OR<sub>e</sub>;
- where R<sub>e</sub> for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -CH<sub>2</sub>-NR<sub>d</sub>R<sub>e</sub>, -W-(CH<sub>2</sub>)<sub>r</sub>-NR<sub>d</sub>R<sub>e</sub>, -W-(CH<sub>2</sub>)<sub>r</sub>-O-alkyl, -W-(CH<sub>2</sub>)<sub>r</sub>-S-alkyl, or -W-(CH<sub>2</sub>)<sub>r</sub>-OH;
- Z<sup>105</sup> for each occurrence is independently a covalent bond or (C<sub>1</sub>-C<sub>6</sub>);
- Z<sup>200</sup> for each occurrence is independently a substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>), substituted or unsubstituted phenyl or substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-phenyl;
- R<sub>d</sub> and R<sub>e</sub> for each occurrence are independently H, alkyl, alkanoyl or SO<sub>2</sub>-alkyl; or R<sub>d</sub>, R<sub>e</sub> and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;
- t for each occurrence is independently an integer from 2 to 6;
- W for each occurrence is independently a direct bond or O, S, S(O), S(O)<sub>2</sub>, or NR<sub>f</sub>, wherein R<sub>f</sub> for each occurrence is independently H or alkyl; or
- R<sub>1</sub> is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;
- R<sub>3</sub> for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a

substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted -C(O)-heteroaryl or substituted or unsubstituted alkoxy;

- A is  $-(C_1-C_6)-$ ,  $-O-$ ,  $-S-$ ,  $-S(O)_p-$ ,  $-N(R)-$ ,  $-N(C(O)OR)-$ ,  $-N(C(O)R)-$ ,  $-N(SO_2R)-$ ,  $-CH_2O-$ ,  $-CH_2S-$ ,  $-CH_2N(R)-$ ,  $-CH(NR)-$ ,  $-CH_2N(C(O)R)-$ ,  $-CH_2N(C(O)OR)-$ ,  $-CH_2N(SO_2R)-$ ,  $-CH(NHR)-$ ,  $-CH(NHC(O)R)-$ ,  $-CH(NHSO_2R)-$ ,  $-CH(NHC(O)OR)-$ ,  $-CH(OC(O)R)-$ ,  $-CH(OC(O)NHR)-$ ,  $-CH=CH-$ ,  $-C(=NOR)-$ ,  $-C(O)-$ ,  $-CH(OR)-$ ,  $-C(O)N(R)-$ ,  $-N(R)C(O)-$ ,  $-N(R)S(O)_p-$ ,  $-OC(O)N(R)-$ ,  $-N(R)-C(O)-(CH_2)_n-N(R)-$ ,  $-N(R)C(O)O-$ ,  $-N(R)-(CH_2)_{n+1}-C(O)-$ ,  $-S(O)_pN(R)-$ ,  $-O-(CR_2)_{n+1}-C(O)-$ ,  $-O-(CR_2)_{n+1}-O-$ ,  $-N(C(O)R)S(O)_p-$ ,  $-N(R)S(O)_pN(R)-$ ,  $-N(R)-C(O)-(CH_2)_n-O-$ ,  $-C(O)N(R)C(O)-$ ,  $-S(O)_pN(R)C(O)-$ ,  $-OS(O)_pN(R)-$ ,  $-N(R)S(O)_pO-$ ,  $-N(R)S(O)_pC(O)-$ ,  $-SO_pN(C(O)R)-$ ,  $-N(R)SO_pN(R)-$ ,  $-C(O)O-$ ,  $-N(R)P(OR_b)O-$ ,  $-N(R)P(OR_b)-$ ,  $-N(R)P(O)(OR_b)O-$ ,  $-N(R)P(O)(OR_b)-$ ,  $-N(C(O)R)P(OR_b)O-$ ,  $-N(C(O)R)P(OR_b)-$ ,  $-N(C(O)R)P(O)(OR_b)O-$ , or  $-N(C(O)R)P(OR_b)-$ ;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

- $R_b$  for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

- in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and  $R_b$  together form a five- or six-membered heterocyclic ring; or

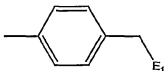
- A is  $NRSO_2$  and R,  $R_a$  and the nitrogen atom together form a substituted or unsubstituted five or six-membered heterocyclic ring fused to ring 1;

or

$Z^{110}-A-Z^{111}$  taken together is a covalent bond; and

- $R_2$  is a) hydrogen; b) substituted or unsubstituted trityl; c) substituted or unsubstituted cycloalkenyl; d) azaheteroaryl substituted with a substituted or unsubstituted alkyl; e) azacycloalkyl which is substituted with one or more substituents selected from substituted or

unsubstituted  $-(C_1-C_6)\text{-alkyl}$ , substituted or unsubstituted  $-C_1-C_6\text{-alkyl-OR}$ , substituted or unsubstituted  $-C(O)-C_1-C_6\text{-alkyl-N(R)}_2$ , substituted or unsubstituted  $-C_1-C_6\text{-alkyl-N(R)}_2$ , substituted or unsubstituted  $-C_1-C_6\text{-alkyl-cycloalkyl}$ , substituted or unsubstituted tetrahydrothienyl, and substituted or unsubstituted tetrahydrothiopyranyl; or f) a group of the formula



wherein  $E_1$  is piperidinyl, piperazinyl, imidazolyl, morpholinyl, pyrrolidinyl, amino, amido, or tetrahydrothiazolyl, and wherein  $E$  is optionally substituted with one or more substituents selected from  $-C_0-C_6\text{-alkyl-OR}$ ,  $-C_1-C_6\text{-alkyl-C(O)OR}$ ,  $-C_1-C_6\text{-alkyl-heteroaryl}$ ,  $-C_1-C_6\text{-alkyl-heterocycloalkyl}$ , and  $-C_1-C_6\text{-alkyl-N(R)}_2$ ;

a is 1 and  $D_1$ ,  $G_1$ ,  $J_1$ ,  $L_1$  and  $M_1$  are each independently selected from the group consisting of  $CR_a$  and  $N$ , provided that at least two of  $D_1$ ,  $G_1$ ,  $J_1$ ,  $L_1$  and  $M_1$  are  $CR_a$ ; or

a is 0, and one of  $D_1$ ,  $G_1$ ,  $L_1$  and  $M_1$  is  $NR_a$ , one of  $D_1$ ,  $G_1$ ,  $L_1$  and  $M_1$  is  $CR_a$  and the remainder are independently selected from the group consisting of  $CR_a$  and  $N$ , wherein  $R_a$  is as defined above;

b is 1 and  $D_2$ ,  $G_2$ ,  $J_2$ ,  $L_2$  and  $M_2$  are each independently selected from the group consisting of  $CR_a$  and  $N$ , provided that at least two of  $D_2$ ,  $G_2$ ,  $J_2$ ,  $L_2$  and  $M_2$  are  $CR_a$ ; or

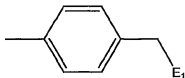
b is 0, and one of  $D_2$ ,  $G_2$ ,  $L_2$  and  $M_2$  is  $NR_a$ , one of  $D_2$ ,  $G_2$ ,  $L_2$  and  $M_2$  is  $CR_a$  and the remainder are independently selected from the group consisting of  $CR_a$  and  $N$ , wherein  $R_a$  is as defined above; and

n for each occurrence is independently an integer from 0 to 6; provided that when  $Z^{110}\text{-A-Z}^{111}$  taken together are a covalent bond, then  $Z^{100}$  is not alkyl; and

provided that when  $Z^{110}\text{-A-Z}^{111}$  taken together are a  $C_1-C_6$  alkyl, then  $Z^{100}$  is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl.

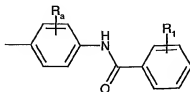
-814-

90. The compound of Claim 89, wherein  $R_2$  is a group represented by the following structural formula:

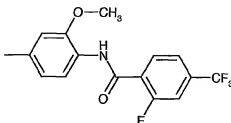


wherein:

- 5 E<sub>1</sub> is selected from the group consisting of -amino-C<sub>1</sub>-C<sub>6</sub>-alkyl-morpholino, -piperidino-(C<sub>1</sub>-C<sub>6</sub>-alkyl-OR), -imidazolyl-C<sub>1</sub>-C<sub>6</sub>-alkyl-C(O)OR, -piperazino-C<sub>1</sub>-C<sub>6</sub>-alkyl-OR, -amino-C<sub>1</sub>-C<sub>6</sub>-alkyl-OR, -pyrrolidino-OR, -amino-C<sub>1</sub>-C<sub>6</sub>-alkyl-imidazolo, -amino-C<sub>1</sub>-C<sub>6</sub>-alkyl-N(R)<sub>2</sub>, -amido-C<sub>1</sub>-C<sub>6</sub>-alkyl-N(R)<sub>2</sub>, tetrahydrothiazolyl, N,N-di-(hydroxy-C<sub>1</sub>-  
10 C<sub>6</sub>-alkyl)amino-, and -piperizino-OR.
91. The compound of Claim 90, wherein:  
E<sub>1</sub> is selected from the group consisting of 4-(2-hydroxyethyl)morpholino, 3-  
hydroxymethylpiperidino, 2-[3-(methylcarboxy)propyl]imidizol-4-yl,  
15 4-(2-hydroxyethyl)piperazino, 2-hydroxyethylamino, 3-hydroxypyrrolidino, 3-imidazolopropylamino, 4-hydroxybutylamino, 3-methoxypropylamino, 3-(N,N-dimethylamino)propylamino, N-[2-(N,N-dimethyl)ethyl]amido, tetrahydrothiazolyl, N,N-di-(2-hydroxyethyl)amino, 4-hydroxypiperizino, and 4-hydroxymethylpiperizino.
- 20
92. The compound of Claim 90, wherein Z<sup>110</sup>-A-Z<sup>111</sup> is -NHC(O)-.
93. The compound of Claim 90, wherein G is a group represented by the following structural formula:
- 25



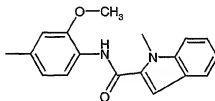
94. The compound of Claim 93, wherein G is represented by the following structural formula:



5

95. The compound of Claim 89, wherein  $R_2$  is an azaheteroaryl substituted with a  $C_1$ - $C_6$  alkyl, wherein the alkyl is optionally substituted with one or more substituents selected from  $RO$ -,  $-C(O)OR$ -,  $-C(O)N(R)_2$ , and  $-N(R)_2$ .
96. The compound of Claim 95, wherein  $R_2$  is 4-(2-hydroxyethyl)pyridin-2-yl, 3-aminomethylpyridin-4-yl or 2-methylimidazol-4-yl.
97. The compound of Claim 96, wherein G is represented by the following formula:

15

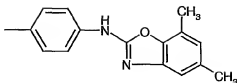


98. The compound of Claim 89, wherein  $R_2$  is a pyrrolidinyl which is substituted with 2-methoxyethyl,  $N,N$ -dimethylaminomethyl,  $N,N$ -dimethylamino-1-oxoethyl, or 2-( $N$ -methylamino)-1-oxopropyl.
99. The compound of Claim 98 wherein G is represented by the following structural formula:

20

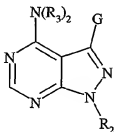


-816-



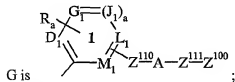
100. The compound of Claim 89, wherein  $R_2$  is a piperidinyl which is substituted with a tetrahydrothiopyranyl, tetrahydrothienyl, 2-(N-methylamino)-2-methyl-1-oxopropyl, 2-methoxyethyl, or cyclopropylmethyl.

101. A compound of Formula (I)

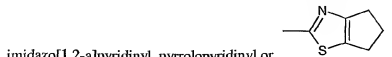


(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:



wherein  $Z^{100}$  is pyrrolidinyl, quinolinyl, quinoxaliny, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, H-pyridinone, 1,1-dioxymethoxythiazolyl, benzoisoxazolyl, alkyl,



imidazo[1,2-a]pyridinyl, pyrrolopyridinyl or wherein all of the foregoing  $Z^{100}$  groups are optionally substituted with  $R_1$ ;

$Z^{110}$  is a covalent bond, or an optionally substituted ( $C_1-C_6$ ) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

$Z^{111}$  is a covalent bond, an optionally substituted ( $C_1-C_6$ ) or an optionally substituted  $-(CH_2)_n$ -cycloalkyl- $(CH_2)_n$ -; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

$R_4$  and  $R_1$  each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN,  $-NO_2$ ,  $-C(O)OH$ ,  $-C(O)H$ , -OH,  $-C(O)O$ -alkyl,  $-C(O)O$ -aryl,  $-C(O)O$ -heteroaryl,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl- $S(O)_p$ -, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl- $S(O)_p$ -, substituted or unsubstituted heteroaryl- $S(O)_p$ -, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio,  $-Z^{105}-C(O)N(R)_2$ ,  $-Z^{105}-N(R)-C(O)-Z^{200}$ ,  $-Z^{105}-N(R)-S(O)_2-Z^{200}$ ,  $-Z^{105}-N(R)-C(O)-N(R)-Z^{200}$ ,  $R_c$  and  $CH_2OR_c$ ;

where  $R_c$  for each occurrence is independently hydrogen, substituted or

unsubstituted alkyl, substituted or unsubstituted aryl,  $-\text{CH}_2-\text{NR}_d\text{R}_e$ ,  $-\text{W}-(\text{CH}_2)_r-\text{NR}_d\text{R}_e$ ,  $-\text{W}-(\text{CH}_2)_r-\text{O}-\text{alkyl}$ ,  $-\text{W}-(\text{CH}_2)_r-\text{S}-\text{alkyl}$ , or  $-\text{W}-(\text{CH}_2)_r-\text{OH}$ ;

$Z^{105}$  for each occurrence is independently a covalent bond or  $(\text{C}_1-\text{C}_6)$ ;

5  $Z^{200}$  for each occurrence is independently a substituted or unsubstituted  $(\text{C}_1-\text{C}_6)$ , substituted or unsubstituted phenyl or substituted or unsubstituted  $-(\text{C}_1-\text{C}_6)$ -phenyl;

$\text{R}_d$  and  $\text{R}_e$  for each occurrence are independently H, alkyl, alkanoyl or  $\text{SO}_2$ -alkyl; or  $\text{R}_d$ ,  $\text{R}_e$  and the nitrogen atom to which they are attached

10 together form a five- or six-membered heterocyclic ring;

$t$  for each occurrence is independently an integer from 2 to 6;

$\text{W}$  for each occurrence is independently a direct bond or O, S,  $\text{S}(\text{O})$ ,  $\text{S}(\text{O})_2$ , or

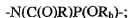
$\text{NR}_f$ , wherein  $\text{R}_f$  for each occurrence is independently H or alkyl; or

15  $\text{R}_1$  is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

$\text{R}_3$  for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted  $-\text{C}(\text{O})$ -alkyl, a substituted or unsubstituted  $-\text{C}(\text{O})$ -aryl, or a substituted or unsubstituted  $-\text{C}(\text{O})$ -heteroaryl or substituted or unsubstituted alkoxy;

20 A is  $-(\text{C}_1-\text{C}_6)-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S}(\text{O})_p-$ ,  $-\text{N}(\text{R})-$ ,  $-\text{N}(\text{C}(\text{O})\text{OR})-$ ,  $-\text{N}(\text{C}(\text{O})\text{R})-$ ,  $-\text{N}(\text{SO}_2\text{R})-$ ,  $-\text{CH}_2\text{O}-$ ,  $-\text{CH}_2\text{S}-$ ,  $-\text{CH}_2\text{N}(\text{R})-$ ,  $-\text{CH}(\text{NR})-$ ,  $-\text{CH}_2\text{N}(\text{C}(\text{O})\text{R})-$ ,  $-\text{CH}_2\text{N}(\text{C}(\text{O})\text{OR})-$ ,  $-\text{CH}_2\text{N}(\text{SO}_2\text{R})-$ ,  $-\text{CH}(\text{NHR})-$ ,  $-\text{CH}(\text{NHC}(\text{O})\text{R})-$ ,  $-\text{CH}(\text{NHSO}_2\text{R})-$ ,  $-\text{CH}(\text{NHC}(\text{O})\text{OR})-$ ,  $-\text{CH}(\text{OC}(\text{O})\text{R})-$ ,  $-\text{CH}(\text{OC}(\text{O})\text{NHR})-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}(=\text{NOR})-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{CH}(\text{OR})-$ ,  $-\text{C}(\text{O})\text{N}(\text{R})-$ ,  $-\text{N}(\text{R})\text{C}(\text{O})-$ ,  $-\text{N}(\text{R})\text{S}(\text{O})_p-$ ,  $-\text{OC}(\text{O})\text{N}(\text{R})-$ ,  $-\text{N}(\text{R})-\text{C}(\text{O})-(\text{CH}_2)_n-\text{N}(\text{R})-$ ,  $-\text{N}(\text{R})\text{C}(\text{O})\text{O}-$ ,  $-\text{N}(\text{R})-(\text{CH}_2)_{n+1}-\text{C}(\text{O})-$ ,  $-\text{S}(\text{O})_p\text{N}(\text{R})-$ ,  $-\text{O}-(\text{CR}_2)_{n+1}-\text{C}(\text{O})-$ ,  $-\text{O}-(\text{CR}_2)_{n+1}-\text{O}-$ ,  $-\text{N}(\text{C}(\text{O})\text{R})\text{S}(\text{O})_p-$ ,  $-\text{N}(\text{R})\text{S}(\text{O})_p\text{N}(\text{R})-$ ,  $-\text{N}(\text{R})-\text{C}(\text{O})-(\text{CH}_2)_n-\text{O}-$ ,  $-\text{C}(\text{O})\text{N}(\text{R})\text{C}(\text{O})-$ ,  $-\text{S}(\text{O})_p\text{N}(\text{R})\text{C}(\text{O})-$ ,  $-\text{OS}(\text{O})_p\text{N}(\text{R})-$ ,  $-\text{N}(\text{R})\text{S}(\text{O})_p\text{O}-$ ,  $-\text{N}(\text{R})\text{S}(\text{O})_p\text{C}(\text{O})-$ ,  $-\text{SO}_p\text{N}(\text{C}(\text{O})\text{R})-$ ,  $-\text{N}(\text{R})\text{SO}_p\text{N}(\text{R})-$ ,  $-\text{C}(\text{O})\text{O}-$ ,  $-\text{N}(\text{R})\text{P}(\text{OR}_b)\text{O}-$ ,  $-\text{N}(\text{R})\text{P}(\text{OR}_b)-$ ,  $-\text{N}(\text{R})\text{P}(\text{O})(\text{OR}_b)\text{O}-$ ,  $-\text{N}(\text{C}(\text{O})\text{R})\text{P}(\text{OR}_b)\text{O}-$ , or

30



where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R<sub>b</sub> for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R<sub>b</sub> together form a five- or six-membered heterocyclic ring; or

A is NRSO<sub>2</sub> and R, R<sub>a</sub> and the nitrogen atom together form a substituted or unsubstituted five or six-membered heterocyclic ring fused to ring 1; or

Z<sup>110</sup>-A-Z<sup>111</sup> taken together is a covalent bond; and

R<sub>2</sub> is H or a group of the formula -Z<sup>101</sup>-Z<sup>102</sup>,

Z<sup>101</sup> is a covalent bond, -(C<sub>1</sub>-C<sub>6</sub>)-, -(C<sub>1</sub>-C<sub>6</sub>)-O-, -(C<sub>1</sub>-C<sub>6</sub>)-C(O)-, -(C<sub>1</sub>-C<sub>6</sub>)-C(O)O-, -(C<sub>1</sub>-C<sub>6</sub>)-C(O)-NH-, -(C<sub>1</sub>-C<sub>6</sub>)-C(O)-N((C<sub>1</sub>-C<sub>6</sub>))- or a substituted or unsubstituted phenyl group;

Z<sup>102</sup> is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, substituted or unsubstituted -N((C<sub>1</sub>-C<sub>6</sub>)-OR)<sub>2</sub>, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-C(O)<sub>2</sub>R, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-C(O)N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or

unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted  $-N(R)-(C_1-C_6)-OR$ , oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  $-C(O)N(R)_2$ , substituted or unsubstituted  $-C(O)-(C_1-C_6)-N(R)_2$ ,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

$R_2$  is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted  $(C_1-C_6)$ -azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl- $N(R)-(C_1-C_6)$ -, substituted or unsubstituted aryl- $N(R)-(C_1-C_6)$ -, substituted or unsubstituted alkyl- $N(R)-(C_1-C_6)$ -, substituted or unsubstituted heteroaryl- $(C_1-C_6)-N(R)$ -, substituted or unsubstituted aryl- $(C_1-C_6)-N(R)$ -, substituted or unsubstituted alkyl- $(C_1-C_6)-N(R)$ -, substituted

- or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;
- a is 1 and D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are CR<sub>a</sub>; or
- a is 0, and one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is NR<sub>a</sub>, one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is CR<sub>a</sub> and the remainder are independently selected from the group consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above;
- b is 1 and D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are CR<sub>a</sub>; or
- b is 0, and one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is NR<sub>a</sub>, one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is CR<sub>a</sub> and the remainder are independently selected from the group consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above; and
- n for each occurrence is independently an integer from 0 to 6; provided that when A is -N(R)-, Z<sup>110</sup> and Z<sup>111</sup> are each a covalent bond, and R<sub>2</sub> is a 3,4-dihydroxytetrahydrofuran-2-yl or a 3,4-diacloxytetrahydrofuran-2-yl, then Z<sup>100</sup> is not alkyl, tetrahydropyranyl, tetrahydrofuran-yl, piperidin-yl or pyrrolidin-yl; provided that when Z<sup>110</sup> and Z<sup>111</sup> are each a covalent bond, and R<sub>2</sub> is a 3,4-dihydroxytetrahydrofuran-2-yl or a 3,4-diacloxytetrahydrofuran-2-yl, Z<sup>100</sup> is a substituted or unsubstituted alkyl, then A is not alkyl, -O-, -C(O)-, -NHC(O)- or -C(O)O-; provided that when Z<sup>110</sup>-A-Z<sup>111</sup> taken together are a covalent bond, then Z<sup>100</sup> is not alkyl;

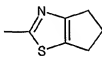
-822-

provided that when  $Z^{110}$ -A- $Z^{111}$  taken together are a  $C_1$ - $C_6$  alkyl, then  $Z^{100}$  is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl; and

provided that when  $R_2$  is a substituted or unsubstituted cyclopentyl,  $Z^{100}$  is an substituted or unsubstituted alkyl,  $Z^{110}$  and  $Z^{111}$  are each a covalent bond, then A is not  $-O-$ ,  $-C(O)O-$ , or  $-N(R)-$ .

102. The compound of Claim 101, wherein  $Z^{100}$  is 2-pyrrolidinyl, 1,2-dihydro-2-oxopyridin-3-yl, benzoisoxazol-3-yl, 1,1-dioxobenzoisothiazol-3-yl,

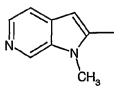
- 10 imidazo[1,2-a]pyridin-2-yl or methylpiperazino)-cyclohexyl.



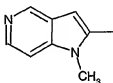
and  $R_2$  is 4-(4-

103. The compound of Claim 102, wherein  $Z^{110}$ -A- $Z^{111}$  is  $-NH-$ .

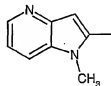
- 15 104. The compound of Claim 101, wherein  $Z^{100}$  is a pyrrolopyridinyl selected from



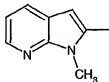
,



,



or



105. The compound of Claim 104, wherein  $Z^{110}$ -A- $Z^{111}$  is  $-NHC(O)-$ .

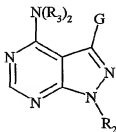
20

106. The compound of Claim 105, wherein  $R_2$  is piperidin-4-yl, N-methylpiperidin-4-yl, N-(prop-2-yl)piperidin-4-yl, N-(imidazol-4-yl-methyl)piperidin-4-yl, N-(2-methylimidazol-4-yl-methyl)piperidin-4-yl, N-

(pyrazol-4-yl-methyl)piperidin-4-yl, N-(2-methoxyethyl)piperidin-4-yl, N-(fur-3-yl-methyl)piperidin-4-yl, N-(tetrahydropyran-4-yl-methyl)piperidin-4-yl, N-(pyrrol-2-yl-methyl)piperidin-4-yl, or N-(2-difluoroethyl)piperidin-4-yl.

5

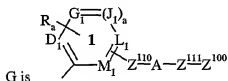
107. A compound of Formula (I)



(I)

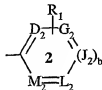
10

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:



G is

15



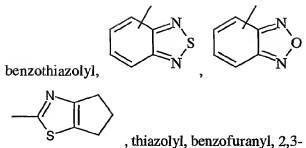
where  $Z^{100}$  is or a group optionally substituted with  $R_1$

selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzo[thienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,

20



-824-



dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranlyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indoliny, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

$Z^{110}$  is a covalent bond, or an optionally substituted ( $C_1-C_6$ ) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

$Z^{111}$  is a covalent bond, an optionally substituted ( $C_1-C_6$ ) or an optionally substituted  $-(CH_2)_n$ -cycloalkyl- $(CH_2)_m$ -; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

$R_a$  and  $R_1$  each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-S(O) $_p$ -, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-S(O) $_p$ -, substituted or unsubstituted heteroaryl-S(O) $_p$ -, and wherein at least one of  $R_a$  and  $R_1$  is not hydrogen;

$R_3$  for each occurrence is, independently, hydrogen, hydroxy, substituted or

unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted -C(O)-heteroaryl or substituted or unsubstituted alkoxy;

- 5 A is  $-(C_1-C_6)-$ ,  $-O-$ ,  $-S-$ ,  $-S(O)_p-$ ,  $-N(R)-$ ,  $-N(C(O)OR)-$ ,  $-N(C(O)R)-$ ,  $-N(SO_2R)-$ ,  $-CH_2O-$ ,  $-CH_2S-$ ,  $-CH_2N(R)-$ ,  $-CH(NR)-$ ,  $-CH_2N(C(O)R)-$ ,  $-CH_2N(C(O)OR)-$ ,  $-CH_2N(SO_2R)-$ ,  $-CH(NHR)-$ ,  $-CH(NHC(O)R)-$ ,  $-CH(NHSO_2R)-$ ,  $-CH(NHC(O)OR)-$ ,  $-CH(OC(O)R)-$ ,  $-CH(OC(O)NHR)-$ ,  $-CH=CH-$ ,  $-C(=NOR)-$ ,  $-C(O)-$ ,  $-CH(OR)-$ ,  $-C(O)N(R)-$ ,  $-N(R)C(O)-$ ,  $-N(R)S(O)_p-$ ,  $-OC(O)N(R)-$ ,  $-N(R)-C(O)-(CH_2)_n-N(R)-$ ,  $-N(R)C(O)O-$ ,  $-N(R)-(CH_2)_{n+1}-C(O)-$ ,  $-S(O)_pN(R)-$ ,  $-O-(CR_2)_{n+1}-C(O)-$ ,  $-O-(CR_2)_{n+1}-O-$ ,  $-N(C(O)R)S(O)_p-$ ,  $-N(R)S(O)_pN(R)-$ ,  $-N(R)-C(O)-(CH_2)_n-O-$ ,  $-C(O)N(R)C(O)-$ ,  $-S(O)_pN(R)C(O)-$ ,  $-OS(O)_pN(R)-$ ,  $-N(R)S(O)_pO-$ ,  $-N(R)S(O)_pC(O)-$ ,  $-SO_pN(C(O)R)-$ ,  $-N(R)SO_pN(R)-$ ,  $-C(O)O-$ ,  $-N(R)P(OR_b)O-$ ,  $-N(R)P(OR_b)-$ ,  $-N(R)P(O)(OR_b)O-$ ,  $-N(R)P(O)(OR_b)-$ ,  $-N(C(O)R)P(OR_b)O-$ ,  $-N(C(O)R)P(OR_b)-$ ,  $-N(C(O)R)P(O)(OR_b)O-$ , or  $-N(C(O)R)P(OR_b)-$ ;
- 10
- 15

where R for each occurrence is independently H, substituted or unsubstituted

- 20 alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

$R_b$  for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

- 25 in a phosphorus containing group, the nitrogen atom, the phosphorus atom,  $R$  and  $R_b$  together form a five- or six-membered heterocyclic ring; or

A is  $NRSO_2$  and  $R$ ,  $R_a$  and the nitrogen atom together form a substituted or unsubstituted five or six-membered heterocyclic ring fused to ring 1;

or

- 30  $Z^{110}-A-Z^{111}$  taken together is a covalent bond; and

$R_2$  is H or a group of the formula  $-Z^{101}-Z^{102}$ ;

$Z^{101}$  is a covalent bond,  $-(C_1-C_6)-$ ,  $-(C_1-C_6)-O-$ ,  $-(C_1-C_6)-C(O)-$ ,  $-(C_1-C_6)-C(O)O-$ ,  $-(C_1-C_6)-C(O)-NH-$ ,  $-(C_1-C_6)-C(O)-N((C_1-C_6))$  or a

substituted or unsubstituted phenyl group;

$Z^{102}$  is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted ( $C_1-C_6$ ), substituted or unsubstituted aryl, substituted or unsubstituted  $-C(O)$ -alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted  $-N(R)-(C_1-C_6)-OR$ , substituted or unsubstituted  $-N((C_1-C_6)-OR)_2$ , substituted or unsubstituted  $-N(R)-(C_1-C_6)-C(O)_2R$ , substituted or unsubstituted  $-(C_1-C_6)-N(R)-(C_1-C_6)-OR$ , substituted or unsubstituted  $-(C_1-C_6)-N(R)-(C_1-C_6)-N(R)_2$ , substituted or unsubstituted  $-(C_1-C_6)-C(O)N(R)-(C_1-C_6)-N(R)_2$ , substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted  $-N(R)-(C_1-C_6)-OR$ , oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  $-C(O)N(R)_2$ , substituted or unsubstituted  $-C(O)-(C_1-C_6)-N(R)_2$ ,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

$R_2$  is a group of the formula  $-B-E$ , wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl,

- substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylene carbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted aryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted alkyl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted heteroaryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted aryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted alkyl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;
- a is 1 and D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are CR<sub>a</sub>; or
- a is 0, and one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is NR<sub>a</sub>, one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is CR<sub>a</sub> and the remainder are independently selected from the group consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above;

b is 1 and  $D_2$ ,  $G_2$ ,  $J_2$ ,  $L_2$  and  $M_2$  are each independently selected from the group consisting of  $CR_a$  and N, provided that at least two of  $D_2$ ,  $G_2$ ,  $J_2$ ,  $L_2$  and  $M_2$  are  $CR_a$ ; or

b is 0, and one of  $D_2$ ,  $G_2$ ,  $L_2$  and  $M_2$  is  $NR_a$ , one of  $D_2$ ,  $G_2$ ,  $L_2$  and  $M_2$  is  $CR_a$  and the remainder are independently selected from the group consisting of  $CR_a$  and N, wherein  $R_a$  is as defined above; and  
n for each occurrence is independently an integer from 0 to 6;

provided that when A is  $-N(R)-$ ,  $Z^{110}$  and  $Z^{111}$  are each a covalent bond, and  $R_2$  is a 3,4-dihydroxytetrahydrofuran-2-yl or a 3,4-diacloxytetrahydrofuran-2-yl, then  $Z^{100}$  is not alkyl, tetrahydropyranyl, tetrahydrofuran-2-yl, piperidinyl or pyrrolidinyl;

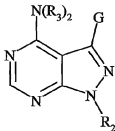
provided that when  $Z^{110}$  and  $Z^{111}$  are each a covalent bond, and  $R_2$  is a 3,4-dihydroxytetrahydrofuran-2-yl or a 3,4-diacloxytetrahydrofuran-2-yl,  $Z^{100}$  is a substituted or unsubstituted alkyl, then A is not alkyl,  $-O-$ ,  $-C(O)-$ ,  $-NHC(O)-$  or  $-C(O)O-$ ;

provided that when  $Z^{110}$ -A- $Z^{111}$  taken together are a covalent bond, then  $Z^{100}$  is not alkyl;

provided that when  $Z^{110}$ -A- $Z^{111}$  taken together are a  $C_1$ - $C_6$  alkyl, then  $Z^{100}$  is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl; and

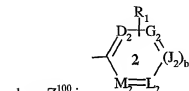
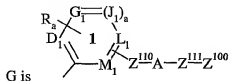
provided that when  $R_2$  is a substituted or unsubstituted cyclopentyl,  $Z^{100}$  is an substituted or unsubstituted alkyl,  $Z^{110}$  and  $Z^{111}$  are each a covalent bond, then A is not  $-O-$ ,  $-C(O)O-$ , or  $-N(R)-$ .

25 108. A compound of Formula (I)



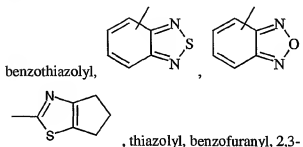
(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:



or a group optionally substituted with  $R_1$

selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,



dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranlyl, tetrahydrofuranlyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

$Z^{110}$  is a covalent bond, or an optionally substituted ( $C_1-C_6$ ) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted

or unsubstituted amino and substituted or unsubstituted phenyl;  
 $Z^{111}$  is a covalent bond, an optionally substituted ( $C_1-C_6$ ) or an optionally  
 substituted  $-(CH_2)_n$ -cycloalkyl- $(CH_2)_n$ -; where the optionally  
 substituted groups are optionally substituted with one or more  
 5 substituents selected from the group consisting of alkyl, CN, OH,  
 halogen,  $NO_2$ ,  $COOH$ , substituted or unsubstituted amino and  
 substituted or unsubstituted phenyl;

$R_1$  and  $R_1$  each represent one or more substituents for each occurrence  
 independently selected from the group consisting of hydrogen,  
 10 halogen,  $-CN$ ,  $-NO_2$ ,  $-C(O)OH$ ,  $-C(O)H$ ,  $-OH$ ,  $-C(O)O$ -alkyl,  $-C(O)O$ -  
 aryl,  $-C(O)O$ -heteroaryl,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heteroaryl,  
 substituted or unsubstituted carboxamido, tetrazolyl,  
 trifluoromethylcarbonylamino, trifluoromethylsulfonamido,  
 substituted or unsubstituted alkyl, substituted or unsubstituted  
 15 cycloalkyl, substituted or unsubstituted alkoxy, substituted or  
 unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted  
 or unsubstituted alkenyl, substituted or unsubstituted aryloxy,  
 substituted or unsubstituted heteroaryloxy, substituted or  
 unsubstituted heteroarylalkoxy, substituted or unsubstituted  
 20 arylalkoxy, substituted or unsubstituted alkyl- $S(O)_p$ -, substituted or  
 unsubstituted alkyl-S-, substituted or unsubstituted aryl- $S(O)_p$ -,  
 substituted or unsubstituted heteroaryl- $S(O)_p$ -, substituted or  
 unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl,  
 substituted or unsubstituted cycloalkylalkyl, substituted or  
 25 unsubstituted alkynyl, substituted or unsubstituted amino, substituted  
 or unsubstituted aminoalkyl, substituted or unsubstituted amido  
 groups, substituted or unsubstituted heteroarylthio, substituted or  
 unsubstituted arylthio,  $-Z^{105}-C(O)N(R)_2$ ,  $-Z^{105}-N(R)-C(O)-Z^{200}$ ,  $-Z^{105}-$   
 $N(R)-S(O)_2-Z^{200}$ ,  $-Z^{105}-N(R)-C(O)-N(R)-Z^{200}$ ,  $R_e$  and  $CH_2OR_e$ ;  
 30 where  $R_e$  for each occurrence is independently hydrogen, substituted or  
 unsubstituted alkyl, substituted or unsubstituted aryl,  $-CH_2-NR_dR_b$ -,  
 $-W-(CH_2)_t-NR_dR_c$ -,  $-W-(CH_2)_t-O$ -alkyl,  $-W-(CH_2)_t-S$ -alkyl, or  $-W-$   
 $(CH_2)_t-OH$ ;

$Z^{105}$  for each occurrence is independently a covalent bond or  $(C_1-C_6)$ ;

$Z^{200}$  for each occurrence is independently a substituted or unsubstituted  $(C_1-C_6)$ , substituted or unsubstituted phenyl or substituted or unsubstituted  $-(C_1-C_6)$ -phenyl;

5  $R_d$  and  $R_e$  for each occurrence are independently H, alkyl, alkanoyl or  $SO_2$ -alkyl; or  $R_d$ ,  $R_e$  and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S,  $S(O)$ ,  $S(O)_2$ , or

10  $NR_f$ , wherein  $R_f$  for each occurrence is independently H or alkyl; or

$R_1$  is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

$R_3$  for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted  $-C(O)$ -alkyl, a

15 substituted or unsubstituted  $-C(O)$ -aryl, or a substituted or unsubstituted  $-C(O)$ -heteroaryl or substituted or unsubstituted alkoxy;

A is  $-(C_1-C_6)-$ ;

R for each occurrence is independently H, substituted or unsubstituted alkyl,

20 substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

p is 1 or 2;

$R_2$  is H or a group of the formula  $-Z^{101}-Z^{102}$ ;

$Z^{101}$  is a covalent bond,  $-(C_1-C_6)-$ ,  $-(C_1-C_6)-O-$ ,  $-(C_1-C_6)-C(O)-$ ,  $-(C_1-C_6)-C(O)O-$ ,  $-(C_1-C_6)-C(O)-NH-$ ,  $-(C_1-C_6)-C(O)-N((C_1-C_6))-$  or a

25 substituted or unsubstituted phenyl group;

$Z^{102}$  is hydrogen; a substituted or unsubstituted alkyl group; a substituted or

unsubstituted cycloalkyl group; a substituted or unsubstituted

cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated

heterocyclic group; or a substituted or unsubstituted, saturated or

30 unsaturated heterobicyclic group; wherein said substituted alkyl,

substituted cycloalkyl, substituted cycloalkenyl, substituted

heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of



hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, substituted or unsubstituted -N((C<sub>1</sub>-C<sub>6</sub>)-OR)<sub>2</sub>, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-C(O)<sub>2</sub>R, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-C(O)N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N(R)<sub>2</sub>, substituted or unsubstituted -C(O)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

R<sub>2</sub> is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylencarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or

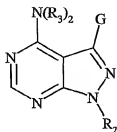
- unsubstituted (C<sub>1</sub>-C<sub>6</sub>)-azacycloalkyl-, substituted or unsubstituted  
 azacycloalkylcarbonyl, substituted or unsubstituted  
 azacycloalkylsulfonyl, substituted or unsubstituted  
 azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C<sub>1</sub>-  
 5 C<sub>6</sub>)-, substituted or unsubstituted aryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or  
 unsubstituted alkyl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted  
 heteroaryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted aryl-(C<sub>1</sub>-C<sub>6</sub>)-  
 N(R)-, substituted or unsubstituted alkyl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted  
 or unsubstituted heteroaryl, substituted or unsubstituted  
 10 heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl,  
 substituted or unsubstituted arylcarbonyl, substituted or unsubstituted  
 heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl,  
 substituted or unsubstituted arylsulfonyl, substituted or unsubstituted  
 heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or  
 15 unsubstituted azacycloalkylcarbonylamino, substituted or  
 unsubstituted heteroarylcarbonylamino, substituted or unsubstituted  
 arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino  
 or substituted or unsubstituted aryl;  
 a is 1 and D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are each independently selected from the  
 20 group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>1</sub>, G<sub>1</sub>,  
 J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are CR<sub>a</sub>; or  
 a is 0, and one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is NR<sub>a</sub>, one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is CR<sub>a</sub>  
 and the remainder are independently selected from the group  
 consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above;  
 25 b is 1 and D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are each independently selected from the  
 group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>2</sub>, G<sub>2</sub>,  
 J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are CR<sub>a</sub>; or  
 b is 0, and one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is NR<sub>a</sub>, one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is CR<sub>a</sub>  
 and the remainder are independently selected from the group  
 consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above; and  
 30 n for each occurrence is independently an integer from 0 to 6;  
 provided that when Z<sup>110</sup>-A-Z<sup>111</sup> taken together are a C<sub>1</sub>-C<sub>6</sub> alkyl, then Z<sup>100</sup> is  
 not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl,

-834-

pyrazinyl, pyridazinyl, furyl or thienyl.

109. A compound of Formula (I)

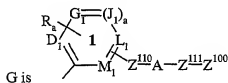
5



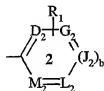
(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-  
 acceptable salts, prodrugs or biologically active metabolites thereof wherein:

10



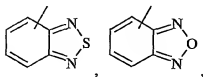
G is

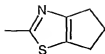


where  $Z^{100}$  is or a group optionally substituted with  $R_1$

selected from the group consisting of pyrrolidinyl, quinolinyl,  
 quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-  
 a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-  
 b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl,  
 thienyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl,

15





, thiazolyl, benzofuranyl, 2,3-

dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl,

tetrahydrofuran, piperidinyl, pyrazolyl, pyrrolyl, pyrrolpyridinyl,

H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl,

5 indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

R<sub>2</sub> and R<sub>1</sub> each represent one or more substituents for each occurrence

independently selected from the group consisting of hydrogen,

10 halogen, -CN, -NO<sub>2</sub>, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl,

substituted or unsubstituted carboxamido, tetrazolyl,

trifluoromethylcarbonylamino, trifluoromethylsulfonamido,

substituted or unsubstituted alkyl, substituted or unsubstituted

15 cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted

20 arylalkoxy, substituted or unsubstituted alkyl-S(O)<sub>p</sub>-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-S(O)<sub>p</sub>-,

substituted or unsubstituted heteroaryl-S(O)<sub>p</sub>-, substituted or

unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl,

substituted or unsubstituted cycloalkylalkyl, substituted or

25 unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z<sup>105</sup>-C(O)N(R)<sub>2</sub>, -Z<sup>105</sup>-N(R)-C(O)-Z<sup>200</sup>, -Z<sup>105</sup>-

N(R)-S(O)<sub>2</sub>-Z<sup>200</sup>, -Z<sup>105</sup>-N(R)-C(O)-N(R)-Z<sup>200</sup>, R<sub>c</sub> and CH<sub>2</sub>OR<sub>c</sub>;

30 where R<sub>c</sub> for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -CH<sub>2</sub>-NR<sub>d</sub>R<sub>e</sub>, -

$W-(CH_2)_r-NR_dR_e$ ,  $-W-(CH_2)_r-O-alkyl$ ,  $-W-(CH_2)_r-S-alkyl$ , or  $-W-(CH_2)_r-OH$ ;

$Z^{105}$  for each occurrence is independently a covalent bond or  $(C_1-C_6)$ ;

$Z^{200}$  for each occurrence is independently a substituted or unsubstituted  $(C_1-C_6)$ , substituted or unsubstituted phenyl or substituted or unsubstituted  $-(C_1-C_6)$ -phenyl;

$R_d$  and  $R_e$  for each occurrence are independently H, alkyl, alkanoyl or  $SO_2$ -alkyl; or  $R_d$ ,  $R_e$  and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

$t$  for each occurrence is independently an integer from 2 to 6;

$W$  for each occurrence is independently a direct bond or O, S,  $S(O)$ ,  $S(O)_2$ , or  $NR_f$ , wherein  $R_f$  for each occurrence is independently H or alkyl; or  $R_1$  is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

$R_3$  for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted  $-C(O)-alkyl$ , a substituted or unsubstituted  $-C(O)-aryl$ , or a substituted or unsubstituted  $-C(O)$ -heteroaryl or substituted or unsubstituted alkoxy;

$R$  for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

$p$  is 1 or 2;

$Z^{110}-A-Z^{111}$  taken together is a covalent bond; and

$R_2$  is H or a group of the formula  $-Z^{101}-Z^{102}$ ;

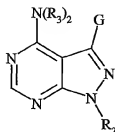
$Z^{101}$  is a covalent bond,  $-(C_1-C_6)-$ ,  $-(C_1-C_6)-O-$ ,  $-(C_1-C_6)-C(O)-$ ,  $-(C_1-C_6)-C(O)O-$ ,  $-(C_1-C_6)-C(O)-NH-$ ,  $-(C_1-C_6)-C(O)-N((C_1-C_6))-$  or a substituted or unsubstituted phenyl group;

$Z^{102}$  is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted

- heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted ( $C_1-C_6$ ), substituted or unsubstituted aryl, substituted or unsubstituted  $-C(O)-$ alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted  $-N(R)-(C_1-C_6)-OR$ , substituted or unsubstituted  $-N((C_1-C_6)-OR)_2$ , substituted or unsubstituted  $-N(R)-(C_1-C_6)-C(O)_2R$ , substituted or unsubstituted  $-(C_1-C_6)-N(R)-(C_1-C_6)-OR$ , substituted or unsubstituted  $-(C_1-C_6)-N(R)-(C_1-C_6)-N(R)_2$ , substituted or unsubstituted  $-(C_1-C_6)-C(O)N(R)-(C_1-C_6)-N(R)_2$ , substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted  $-N(R)-(C_1-C_6)-OR$ , oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  $-C(O)N(R)_2$ , substituted or unsubstituted  $-C(O)-(C_1-C_6)-N(R)_2$ ,  $-C(O)-alkyl$ ,  $-C(O)-aryl$ ,  $-C(O)-heteroaryl$ , substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or
- $R_2$  is a group of the formula  $-B-E$ , wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylene carbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or

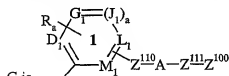
- unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted aryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted alkyl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted heteroaryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted aryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted alkyl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;
- a is 1 and D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are CR<sub>a</sub>; or
- a is 0, and one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is NR<sub>a</sub>, one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is CR<sub>a</sub> and the remainder are independently selected from the group consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above;
- b is 1 and D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are CR<sub>a</sub>; or
- b is 0, and one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is NR<sub>a</sub>, one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is CR<sub>a</sub> and the remainder are independently selected from the group consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above; and
- n for each occurrence is independently an integer from 0 to 6.

110. A compound of Formula (I)

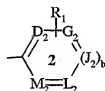


(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

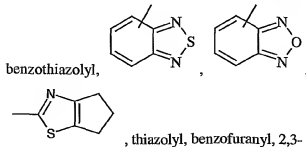


G is



where  $Z^{100}$  is or a group optionally substituted with  $R_1$

selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxaliny, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,



, thiazolyl, benzofuranyl, 2,3-



dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranlyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxobenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

$Z^{110}$  is a covalent bond, or an optionally substituted ( $C_1-C_6$ ) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

$Z^{111}$  is a covalent bond, an optionally substituted ( $C_1-C_6$ ) or an optionally substituted  $-(CH_2)_n$ -cycloalkyl- $(CH_2)_n$ -; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

$R_n$  and  $R_1$  each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, - $NO_2$ , -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-S(O) $_p$ -, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-S(O) $_p$ -, substituted or unsubstituted heteroaryl-S(O) $_p$ -, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or

- unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio,  $-Z^{105}-C(O)N(R)_2$ ,  $-Z^{105}-N(R)-C(O)-Z^{200}$ ,  $-Z^{105}-N(R)-S(O)_2-Z^{200}$ ,  $-Z^{105}-N(R)-C(O)-N(R)-Z^{200}$ ,  $R_c$  and  $CH_2OR_c$ ;
- where  $R_c$  for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl,  $-CH_2-NR_dR_e$ ,  $-W-(CH_2)_t-NR_dR_e$ ,  $-W-(CH_2)_t-O$ -alkyl,  $-W-(CH_2)_t-S$ -alkyl, or  $-W-(CH_2)_t-OH$ ;
- $Z^{105}$  for each occurrence is independently a covalent bond or  $(C_1-C_6)$ ;
- $Z^{200}$  for each occurrence is independently a substituted or unsubstituted  $(C_1-C_6)$ , substituted or unsubstituted phenyl or substituted or unsubstituted  $-(C_1-C_6)$ -phenyl;
- $R_d$  and  $R_e$  for each occurrence are independently H, alkyl, alkanoyl or  $SO_2$ -alkyl; or  $R_d$ ,  $R_e$  and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;
- $t$  for each occurrence is independently an integer from 2 to 6;
- $W$  for each occurrence is independently a direct bond or O, S,  $S(O)$ ,  $S(O)_2$ , or  $NR_f$ , wherein  $R_f$  for each occurrence is independently H or alkyl; or
- $R_1$  is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;
- $R_3$  for each occurrence is, independently, substituted or unsubstituted  $-C(O)$ -alkyl, a substituted or unsubstituted  $-C(O)$ -aryl, or a substituted or unsubstituted  $-C(O)$ -heteroaryl.
- A is  $-(C_1-C_6)-$ ,  $-O-$ ,  $-S-$ ,  $-S(O)_p-$ ,  $-N(R)-$ ,  $-N(C(O)OR)-$ ,  $-N(C(O)R)-$ ,  $-N(SO_2R)-$ ,  $-CH_2O-$ ,  $-CH_2S-$ ,  $-CH_2N(R)-$ ,  $-CH(NR)-$ ,  $-CH_2N(C(O)R)-$ ,  $-CH_2N(C(O)OR)-$ ,  $-CH_2N(SO_2R)-$ ,  $-CH(NHR)-$ ,  $-CH(NHC(O)R)-$ ,  $-CH(NHSO_2R)-$ ,  $-CH(NHC(O)OR)-$ ,  $-CH(OC(O)R)-$ ,  $-CH(OC(O)NHR)-$ ,  $-CH=CH-$ ,  $-C(=NOR)-$ ,  $-C(O)-$ ,  $-CH(OR)-$ ,  $-C(O)N(R)-$ ,  $-N(R)C(O)-$ ,  $-N(R)S(O)_p-$ ,  $-OC(O)N(R)-$ ,  $-N(R)-C(O)-(CH_2)_n-N(R)-$ ,  $-N(R)C(O)O-$ ,  $-N(R)-(CH_2)_{n+1}-C(O)-$ ,  $-S(O)_pN(R)-$ ,  $-O-(CR_2)_{n+1}-C(O)-$ ,  $-O-(CR_2)_{n+1}-O-$ ,  $-N(C(O)R)S(O)_p-$ ,  $-N(R)S(O)_pN(R)-$ ,  $-N(R)-C(O)-(CH_2)_n-O-$ ,  $-C(O)N(R)C(O)-$ ,  $-$

-842-

$S(O)_pN(R)C(O)-$ ;  $-OS(O)_pN(R)-$ ;  $-N(R)S(O)_pO-$ ;  $-N(R)S(O)_pC(O)-$ ;  $-SO_pN(C(O)R)-$ ;  $-N(R)SO_pN(R)-$ ;  $-C(O)O-$ ;  $-N(R)P(OR_b)O-$ ;  $-N(R)P(OR_b)-$ ;  $-N(R)P(O)(OR_b)O-$ ;  $-N(R)P(O)(OR_b)-$ ;  $-N(C(O)R)P(OR_b)O-$ ;  $-N(C(O)R)P(OR_b)-$ ;  $-N(C(O)R)P(O)(OR_b)O-$ , or  $-N(C(O)R)P(OR_b)-$ ;

5

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

$R_b$  for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

10

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and  $R_b$  together form a five- or six-membered heterocyclic ring; or

15

$A$  is  $NRSO_2$  and R,  $R_a$  and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1; or

$Z^{110}-A-Z^{111}$  taken together is a covalent bond; and

$R_2$  is H or a group of the formula  $-Z^{101}-Z^{102}$ ;

20

$Z^{101}$  is a covalent bond,  $-(C_1-C_6)-$ ,  $-(C_1-C_6)-O-$ ,  $-(C_1-C_6)-C(O)-$ ,  $-(C_1-C_6)-C(O)O-$ ,  $-(C_1-C_6)-C(O)-NH-$ ,  $-(C_1-C_6)-C(O)-N((C_1-C_6))-$  or a substituted or unsubstituted phenyl group;

$Z^{102}$  is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted  $(C_1-C_6)$ , substituted or unsubstituted aryl, substituted or unsubstituted  $-C(O)-$  alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted  $-N(R)-(C_1-C_6)-OR$ , substituted or unsubstituted  $-N((C_1-C_6))-$

30

OR)<sub>2</sub>, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-C(O)<sub>2</sub>R, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-C(O)N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N(R)<sub>2</sub>, substituted or unsubstituted -C(O)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

R<sub>2</sub> is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylencarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C<sub>1</sub>-

- $C_6$ )-, substituted or unsubstituted aryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted alkyl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted heteroaryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted aryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted alkyl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;
- a is 1 and D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are CR<sub>a</sub>; or
- a is 0, and one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is NR<sub>a</sub>, one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is CR<sub>a</sub> and the remainder are independently selected from the group consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above;
- b is 1 and D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are CR<sub>a</sub>; or
- b is 0, and one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is NR<sub>a</sub>, one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is CR<sub>a</sub> and the remainder are independently selected from the group consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above; and
- n for each occurrence is independently an integer from 0 to 6;
- provided that when A is -N(R)-, Z<sup>110</sup> and Z<sup>111</sup> are each a covalent bond, and R<sub>2</sub> is a 3,4-dihydroxytetrahydrofurfur-2-yl or a 3,4-diacyloxytetrahydrofurfur-2-yl, then Z<sup>100</sup> is not alkyl, tetrahydropyranyl, tetrahydrofuran-yl, piperidinyl or pyrrolidinyl;
- provided that when Z<sup>110</sup> and Z<sup>111</sup> are each a covalent bond, and R<sub>2</sub> is a 3,4-dihydroxytetrahydrofurfur-2-yl or a 3,4-diacyloxytetrahydrofurfur-2-yl, Z<sup>100</sup>

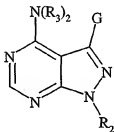
is a substituted or unsubstituted alkyl, then A is not alkyl, -O-, -C(O)-, -NHC(O)- or -C(O)O-;

provided that when  $Z^{110}$ -A- $Z^{111}$  taken together are a covalent bond, then  $Z^{100}$  is not alkyl;

provided that when  $Z^{110}$ -A- $Z^{111}$  taken together are a  $C_1$ - $C_6$  alkyl, then  $Z^{100}$  is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl; and

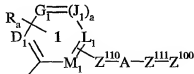
provided that when  $R_2$  is a substituted or unsubstituted cyclopentyl,  $Z^{100}$  is an substituted or unsubstituted alkyl,  $Z^{110}$  and  $Z^{111}$  are each a covalent bond, then A is not -O-, -C(O)O-, or -N(R)-.

111. A compound of Formula (I)

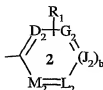


(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:



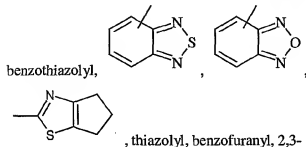
G is



where  $Z^{100}$  is or a group optionally substituted with  $R_1$  selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl,

quinolinyl, quinoxaliny, quinazoliny, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,

5



10

dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranly, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

15

$Z^{110}$  is a covalent bond, or an optionally substituted ( $C_1-C_6$ ) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

20

$Z^{111}$  is a covalent bond, an optionally substituted ( $C_1-C_6$ ) or an optionally substituted  $-(CH_2)_n$ -cycloalkyl- $-(CH_2)_n$ -; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

25

$R_3$  and  $R_1$  each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN,  $-NO_2$ ,  $-C(O)OH$ ,  $-C(O)H$ , -OH,  $-C(O)O$ -alkyl,  $-C(O)O$ -aryl,  $-C(O)O$ -heteroaryl,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted

- cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-S(O)<sub>p</sub>-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-S(O)<sub>p</sub>-, substituted or unsubstituted heteroaryl-S(O)<sub>p</sub>-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z<sup>105</sup>-C(O)N(R)<sub>2</sub>, -Z<sup>105</sup>-N(R)-C(O)-Z<sup>200</sup>, -Z<sup>105</sup>-N(R)-S(O)<sub>2</sub>-Z<sup>200</sup>, -Z<sup>105</sup>-N(R)-C(O)-N(R)-Z<sup>200</sup>, R<sub>c</sub> and CH<sub>2</sub>OR<sub>c</sub>;
- where R<sub>c</sub> for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -CH<sub>2</sub>-NR<sub>d</sub>R<sub>e</sub>, -W-(CH<sub>2</sub>)<sub>t</sub>-NR<sub>d</sub>R<sub>e</sub>, -W-(CH<sub>2</sub>)<sub>t</sub>-O-alkyl, -W-(CH<sub>2</sub>)<sub>t</sub>-S-alkyl, or -W-(CH<sub>2</sub>)<sub>t</sub>-OH;
- Z<sup>105</sup> for each occurrence is independently a covalent bond or (C<sub>1</sub>-C<sub>6</sub>);
- Z<sup>200</sup> for each occurrence is independently a substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>), substituted or unsubstituted phenyl or substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-phenyl;
- R<sub>4</sub> and R<sub>e</sub> for each occurrence are independently H, alkyl, alkanoyl or SO<sub>2</sub>-alkyl; or R<sub>d</sub>, R<sub>e</sub> and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;
- t for each occurrence is independently an integer from 2 to 6;
- W for each occurrence is independently a direct bond or O, S, S(O), S(O)<sub>2</sub>, or NR<sub>f</sub>, wherein R<sub>f</sub> for each occurrence is independently H or alkyl; or
- R<sub>1</sub> is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;
- R<sub>3</sub> for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a



substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted -C(O)-heteroaryl or substituted or unsubstituted alkoxy;

- A is  $-(C_1-C_6)-$ ,  $-O-$ ,  $-S-$ ,  $-S(O)_p-$ ,  $-N(R)-$ ,  $-N(C(O)OR)-$ ,  $-N(C(O)R)-$ ,  $-N(SO_2R)-$ ,  $-CH_2O-$ ,  $-CH_2S-$ ,  $-CH_2N(R)-$ ,  $-CH(NR)-$ ,  $-CH_2N(C(O)R)-$ ,  $-CH_2N(C(O)OR)-$ ,  $-CH_2N(SO_2R)-$ ,  $-CH(NHR)-$ ,  $-CH(NHC(O)R)-$ ,  $-CH(NHSO_2R)-$ ,  $-CH(NHC(O)OR)-$ ,  $-CH(OC(O)R)-$ ,  $-CH(OC(O)NHR)-$ ,  $-CH=CH-$ ,  $-C(=NOR)-$ ,  $-C(O)-$ ,  $-CH(OR)-$ ,  $-C(O)N(R)-$ ,  $-N(R)C(O)-$ ,  $-N(R)S(O)_p-$ ,  $-OC(O)N(R)-$ ,  $-N(R)-C(O)-(CH_2)_n-N(R)-$ ,  $-N(R)C(O)O-$ ,  $-N(R)-(CH_2)_{n+1}-C(O)-$ ,  $-S(O)_pN(R)-$ ,  $-O-(CR_2)_{n+1}-C(O)-$ ,  $-O-(CR_2)_{n+1}-O-$ ,  $-N(C(O)R)S(O)_p-$ ,  $-N(R)S(O)_pN(R)-$ ,  $-N(R)-C(O)-(CH_2)_n-O-$ ,  $-C(O)N(R)C(O)-$ ,  $-S(O)_pN(R)C(O)-$ ,  $-OS(O)_pN(R)-$ ,  $-N(R)S(O)_pO-$ ,  $-N(R)S(O)_pC(O)-$ ,  $-SO_pN(C(O)R)-$ ,  $-N(R)SO_pN(R)-$ ,  $-C(O)O-$ ,  $-N(R)P(OR_b)O-$ ,  $-N(R)P(OR_b)-$ ,  $-N(R)P(O)(OR_b)O-$ ,  $-N(R)P(O)(OR_b)-$ ,  $-N(C(O)R)P(OR_b)O-$ ,  $-N(C(O)R)P(OR_b)-$ ,  $-N(C(O)R)P(O)(OR_b)O-$ , or  $-N(C(O)R)P(OR_b)-$ ;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

- R<sub>b</sub> for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

- in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R<sub>b</sub> together form a five- or six-membered heterocyclic ring; or  
A is NRSO<sub>2</sub> and R, R<sub>a</sub> and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1;

or

- Z<sup>110</sup>-A-Z<sup>111</sup> taken together is a covalent bond; and  
R<sub>2</sub> is a group of the formula  $-Z^{101}-Z^{102}$ ;  
Z<sup>101</sup> is a covalent bond,  $-(C_1-C_6)-$ ,  $-(C_1-C_6)-O-$ ,  $-(C_1-C_6)-C(O)-$ ,  $-(C_1-C_6)-C(O)O-$ ,  $-(C_1-C_6)-C(O)-NH-$ ,  $-(C_1-C_6)-C(O)-N((C_1-C_6))-$  or a substituted or unsubstituted phenyl group;

$Z^{102}$  is a substituted or unsubstituted cycloalkenyl, wherein said substituted cycloalkenyl has one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, substituted or unsubstituted -N((C<sub>1</sub>-C<sub>6</sub>)-OR)<sub>2</sub>, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-C(O)<sub>2</sub>R, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-C(O)N(R)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted -N(R)-(C<sub>1</sub>-C<sub>6</sub>)-OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N(R)<sub>2</sub>, substituted or unsubstituted -C(O)-(C<sub>1</sub>-C<sub>6</sub>)-N(R)<sub>2</sub>, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl;

a is 1 and D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>1</sub>, G<sub>1</sub>, J<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> are CR<sub>a</sub>; or

a is 0, and one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is NR<sub>a</sub>, one of D<sub>1</sub>, G<sub>1</sub>, L<sub>1</sub> and M<sub>1</sub> is CR<sub>a</sub> and the remainder are independently selected from the group consisting of CR<sub>a</sub> and N, wherein R<sub>a</sub> is as defined above;

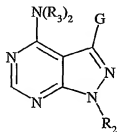
b is 1 and D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are each independently selected from the group consisting of CR<sub>a</sub> and N, provided that at least two of D<sub>2</sub>, G<sub>2</sub>, J<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> are CR<sub>a</sub>; or

b is 0, and one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is NR<sub>a</sub>, one of D<sub>2</sub>, G<sub>2</sub>, L<sub>2</sub> and M<sub>2</sub> is CR<sub>a</sub>

-850-

and the remainder are independently selected from the group consisting of  $CR_a$  and N, wherein  $R_a$  is as defined above; and n for each occurrence is independently an integer from 0 to 6.

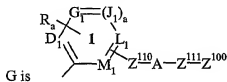
5 112. A compound of Formula (I)



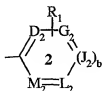
(I)

10

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:



G is

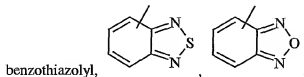


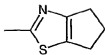
15

where  $Z^{100}$  is

a group optionally substituted with  $R_1$  selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinoliny, quinoxaliny, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,

20





, thiazolyl, benzofuranyl, 2,3-

dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl,  
 tetrahydrofuranlyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolpyridinyl,  
 H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl,  
 5 indolynyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-  
 dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-  
 oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

$Z^{110}$  is a covalent bond, or an optionally substituted ( $C_1-C_6$ ) which is  
 optionally substituted with one or more substituents selected from the  
 10 group consisting of alkyl, CN, OH, halogen,  $NO_2$ , COOH, substituted  
 or unsubstituted amino and substituted or unsubstituted phenyl;

$Z^{111}$  is a covalent bond, an optionally substituted ( $C_1-C_6$ ) or an optionally  
 substituted  $-(CH_2)_n$ -cycloalkyl- $-(CH_2)_n$ -; where the optionally  
 substituted groups are optionally substituted with one or more  
 15 substituents selected from the group consisting of alkyl, CN, OH,  
 halogen,  $NO_2$ , COOH, substituted or unsubstituted amino and  
 substituted or unsubstituted phenyl;

$R_4$  and  $R_1$  each represent one or more substituents for each occurrence  
 independently selected from the group consisting of hydrogen,  
 20 halogen, -CN,  $-NO_2$ ,  $-C(O)OH$ ,  $-C(O)H$ ,  $-OH$ ,  $-C(O)O$ -alkyl,  $-C(O)O$ -  
 aryl,  $-C(O)O$ -heteroaryl,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heteroaryl,  
 substituted or unsubstituted carboxamido, tetrazolyl,  
 trifluoromethylcarbonylamino, trifluoromethylsulfonamido,  
 substituted or unsubstituted alkyl, substituted or unsubstituted  
 25 cycloalkyl, substituted or unsubstituted alkoxy, substituted or  
 unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted  
 or unsubstituted alkenyl, substituted or unsubstituted aryloxy,  
 substituted or unsubstituted heteroaryloxy, substituted or  
 unsubstituted heteroarylalkoxy, substituted or unsubstituted  
 30 arylalkoxy, substituted or unsubstituted alkyl- $S(O)_p$ -, substituted or  
 unsubstituted alkyl-S-, substituted or unsubstituted aryl- $S(O)_p$ -,

- substituted or unsubstituted heteroaryl-S(O)<sub>p</sub>-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z<sup>105</sup>-C(O)N(R)<sub>2</sub>-, -Z<sup>105</sup>-N(R)-C(O)-Z<sup>200</sup>-, -Z<sup>105</sup>-N(R)-S(O)<sub>2</sub>-Z<sup>200</sup>-, -Z<sup>105</sup>-N(R)-C(O)-N(R)-Z<sup>200</sup>-, R<sub>c</sub> and CH<sub>2</sub>OR<sub>c</sub>;
- where R<sub>c</sub> for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -CH<sub>2</sub>-NR<sub>d</sub>R<sub>e</sub>-, W-(CH<sub>2</sub>)<sub>r</sub>-NR<sub>d</sub>R<sub>e</sub>-, -W-(CH<sub>2</sub>)<sub>r</sub>-O-alkyl, -W-(CH<sub>2</sub>)<sub>r</sub>-S-alkyl, or -W-(CH<sub>2</sub>)<sub>r</sub>-OH;
- Z<sup>105</sup> for each occurrence is independently a covalent bond or (C<sub>1</sub>-C<sub>6</sub>);
- Z<sup>200</sup> for each occurrence is independently a substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>), substituted or unsubstituted phenyl or substituted or unsubstituted -(C<sub>1</sub>-C<sub>6</sub>)-phenyl;
- R<sub>d</sub> and R<sub>e</sub> for each occurrence are independently H, alkyl, alkanoyl or SO<sub>2</sub>-alkyl; or R<sub>d</sub>, R<sub>e</sub> and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;
- t for each occurrence is independently an integer from 2 to 6;
- W for each occurrence is independently a direct bond or O, S, S(O), S(O)<sub>2</sub>, or NR<sub>f</sub>, wherein R<sub>f</sub> for each occurrence is independently H or alkyl; or
- R<sub>1</sub> is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;
- R<sub>3</sub> for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted -C(O)-heteroaryl or substituted or unsubstituted alkoxy;
- A is -(C<sub>1</sub>-C<sub>6</sub>)-, -O-, -S-, -S(O)<sub>p</sub>-, -N(R)-, -N(C(O)OR)-, -N(C(O)R)-, -N(SO<sub>2</sub>R)-, -CH<sub>2</sub>O-, -CH<sub>2</sub>S-, -CH<sub>2</sub>N(R)-, -CH(NR)-, -CH<sub>2</sub>N(C(O)R)-, -CH<sub>2</sub>N(C(O)OR)-, -CH<sub>2</sub>N(SO<sub>2</sub>R)-, -CH(NHR)-, -CH(NHC(O)R)-, -CH(NHSO<sub>2</sub>R)-, -CH(NHC(O)OR)-, -CH(OC(O)R)-, -

$\text{CH}(\text{OC}(\text{O})\text{NHR})$ -,  $-\text{CH}=\text{CH}$ -,  $-\text{C}(=\text{NOR})$ -,  $-\text{C}(\text{O})$ -,  $-\text{CH}(\text{OR})$ -,  $-\text{C}(\text{O})\text{N}(\text{R})$ -,  $-\text{N}(\text{R})\text{C}(\text{O})$ -,  $-\text{N}(\text{R})\text{S}(\text{O})_p$ -,  $-\text{OC}(\text{O})\text{N}(\text{R})$ -,  $-\text{N}(\text{R})-\text{C}(\text{O})-(\text{CH}_2)_n-\text{N}(\text{R})$ -,  $-\text{N}(\text{R})\text{C}(\text{O})\text{O}$ -,  $-\text{N}(\text{R})-(\text{CH}_2)_{n+1}-\text{C}(\text{O})$ -,  $-\text{S}(\text{O})_p\text{N}(\text{R})$ -,  $-\text{O}-(\text{CR}_2)_{n+1}-\text{C}(\text{O})$ -,  $-\text{O}-(\text{CR}_2)_{n+1}-\text{O}$ -,  $-\text{N}(\text{C}(\text{O})\text{R})\text{S}(\text{O})_p$ -,  
 5  $-\text{N}(\text{R})\text{S}(\text{O})_p\text{N}(\text{R})$ -,  $-\text{N}(\text{R})-\text{C}(\text{O})-(\text{CH}_2)_n-\text{O}$ -,  $-\text{C}(\text{O})\text{N}(\text{R})\text{C}(\text{O})$ -,  $-\text{S}(\text{O})_p\text{N}(\text{R})\text{C}(\text{O})$ -,  $-\text{OS}(\text{O})_p\text{N}(\text{R})$ -,  $-\text{N}(\text{R})\text{S}(\text{O})_p\text{O}$ -,  $-\text{N}(\text{R})\text{S}(\text{O})_p\text{C}(\text{O})$ -,  $-\text{SO}_p\text{N}(\text{C}(\text{O})\text{R})$ -,  $-\text{N}(\text{R})\text{SO}_p\text{N}(\text{R})$ -,  $-\text{C}(\text{O})\text{O}$ -,  $-\text{N}(\text{R})\text{P}(\text{OR}_b)\text{O}$ -,  $-\text{N}(\text{R})\text{P}(\text{OR}_b)$ -,  $-\text{N}(\text{R})\text{P}(\text{O})(\text{OR}_b)\text{O}$ -,  $-\text{N}(\text{R})\text{P}(\text{O})(\text{OR}_b)$ -,  
 10  $-\text{N}(\text{C}(\text{O})\text{R})\text{P}(\text{OR}_b)\text{O}$ -,  $-\text{N}(\text{C}(\text{O})\text{R})\text{P}(\text{OR}_b)$ -,  $-\text{N}(\text{C}(\text{O})\text{R})\text{P}(\text{O})(\text{OR}_b)\text{O}$ -, or  $-\text{N}(\text{C}(\text{O})\text{R})\text{P}(\text{OR}_b)$ -,

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

$\text{R}_b$  for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted  
 15 cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and  $\text{R}_b$  together form a five- or six-membered heterocyclic ring; or

A is  $\text{NRSO}_2$  and R,  $\text{R}_a$  and the nitrogen atom together form a substituted or  
 20 unsubstituted five or-six-membered heterocyclic ring fused to ring 1;  
 or

$\text{Z}^{110}-\text{A}-\text{Z}^{111}$  taken together is a covalent bond; and

$\text{R}_2$  is a group of the formula  $-\text{Z}^{101}-\text{Z}^{102}$ ;

$\text{Z}^{101}$  is a covalent bond,  $-(\text{C}_1-\text{C}_6)$ -,  $-(\text{C}_1-\text{C}_6)-\text{O}$ -,  $-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})$ -,  $-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})\text{O}$ -,  $-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})-\text{NH}$ -,  $-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})-\text{N}((\text{C}_1-\text{C}_6))$ - or a  
 25 substituted or unsubstituted phenyl group;

$\text{Z}^{102}$  is a substituted, saturated or unsaturated heterocyclic group; or a

substituted, saturated or unsaturated heterobicyclic group; wherein  
 said substituted heterocyclic and substituted heterobicyclic group  
 30 have one or more substituents each independently selected from the  
 group consisting of nitro, halo, substituted or unsubstituted  $(\text{C}_1-\text{C}_6)$ ,  
 substituted or unsubstituted aryl, substituted or unsubstituted  $-\text{C}(\text{O})$ -  
 alkyl, substituted or unsubstituted  $-\text{N}(\text{R})-(\text{C}_1-\text{C}_6)-\text{OR}$ , substituted or

- unsubstituted  $-\text{N}((\text{C}_1-\text{C}_6)_2\text{-OR})_2$ , substituted or unsubstituted  $-\text{N}(\text{R})-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})_2\text{R}$ , substituted or unsubstituted  $-(\text{C}_1-\text{C}_6)-\text{N}(\text{R})-(\text{C}_1-\text{C}_6)-\text{OR}$ , substituted or unsubstituted  $-(\text{C}_1-\text{C}_6)-\text{N}(\text{R})-(\text{C}_1-\text{C}_6)-\text{N}(\text{R})_2$ , substituted or unsubstituted  $-(\text{C}_1-\text{C}_6)-\text{C}(\text{O})\text{N}(\text{R})-(\text{C}_1-\text{C}_6)-\text{N}(\text{R})_2$ , substituted or unsubstituted  $-\text{N}(\text{R})-(\text{C}_1-\text{C}_6)-\text{OR}$ , and a substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  $-\text{C}(\text{O})\text{N}(\text{R})_2$ , substituted or unsubstituted  $-\text{C}(\text{O})-(\text{C}_1-\text{C}_6)-\text{N}(\text{R})_2$ ,  $-\text{C}(\text{O})$ -alkyl,  $-\text{C}(\text{O})$ -aryl,  $-\text{C}(\text{O})$ -heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl;
- 5 a is 1 and  $\text{D}_1$ ,  $\text{G}_1$ ,  $\text{J}_1$ ,  $\text{L}_1$  and  $\text{M}_1$  are each independently selected from the group consisting of  $\text{CR}_a$  and N, provided that at least two of  $\text{D}_1$ ,  $\text{G}_1$ ,  $\text{J}_1$ ,  $\text{L}_1$  and  $\text{M}_1$  are  $\text{CR}_a$ ; or
- 10 a is 0, and one of  $\text{D}_1$ ,  $\text{G}_1$ ,  $\text{L}_1$  and  $\text{M}_1$  is  $\text{NR}_a$ , one of  $\text{D}_1$ ,  $\text{G}_1$ ,  $\text{L}_1$  and  $\text{M}_1$  is  $\text{CR}_a$  and the remainder are independently selected from the group consisting of  $\text{CR}_a$  and N, wherein  $\text{R}_a$  is as defined above;
- 15 b is 1 and  $\text{D}_2$ ,  $\text{G}_2$ ,  $\text{J}_2$ ,  $\text{L}_2$  and  $\text{M}_2$  are each independently selected from the group consisting of  $\text{CR}_a$  and N, provided that at least two of  $\text{D}_2$ ,  $\text{G}_2$ ,  $\text{J}_2$ ,  $\text{L}_2$  and  $\text{M}_2$  are  $\text{CR}_a$ ; or
- 20 b is 0, and one of  $\text{D}_2$ ,  $\text{G}_2$ ,  $\text{L}_2$  and  $\text{M}_2$  is  $\text{NR}_a$ , one of  $\text{D}_2$ ,  $\text{G}_2$ ,  $\text{L}_2$  and  $\text{M}_2$  is  $\text{CR}_a$  and the remainder are independently selected from the group consisting of  $\text{CR}_a$  and N, wherein  $\text{R}_a$  is as defined above;
- 25 n for each occurrence is independently an integer from 0 to 6; provided that when A is  $-\text{N}(\text{R})-$ ,  $\text{Z}^{110}$  and  $\text{Z}^{111}$  are each a covalent bond, and  $\text{R}_2$  is a 3,4-diacyloxytetrahydrofuran-2-yl, then  $\text{Z}^{100}$  is not alkyl, tetrahydropyranyl, tetrahydrofuran-2-yl, piperidinyl or pyrrolidinyl;
- 30 provided that when  $\text{Z}^{110}$  and  $\text{Z}^{111}$  are each a covalent bond, and  $\text{R}_2$  is a 3,4-diacyloxytetrahydrofuran-2-yl,  $\text{Z}^{100}$  is a substituted or unsubstituted alkyl, then A is not alkyl,  $-\text{O}-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{NHC}(\text{O})-$  or  $-\text{C}(\text{O})\text{O}-$ ;

provided that when  $Z^{110}$ -A- $Z^{111}$  taken together are a covalent bond, then  $Z^{100}$  is not alkyl; and

provided that when  $Z^{110}$ -A- $Z^{111}$  taken together are a  $C_1$ - $C_6$  alkyl, then  $Z^{100}$  is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl.

- 5
113. A method of inhibiting one or more protein kinase activity in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.
- 10
114. The method of Claim 113 wherein said protein kinase is selected from the group consisting of KDR, FGFR-1, PDGFR $\beta$ , PDGFR $\alpha$ , IGF-1R, c-Met, Flt-1, Flt-4, TIE-2, TIE-1, Lck, Src, fyn, Lyn, Blk, hck, fgr and yes.
- 15
115. A method of affecting hyperproliferative disorders in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.
- 20
116. A method of affecting angiogenesis in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.
- 25
117. The method of Claim 113 wherein the protein kinase is a protein serine/threonine kinase or a protein tyrosine kinase.
- 30
118. A method of treating one or more ulcers in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.

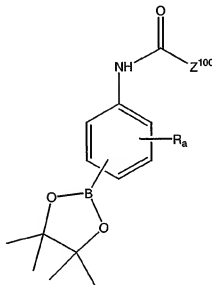


119. The method of Claim 118 wherein the ulcer or ulcers are caused by a bacterial or fungal infection; or the ulcer or ulcers are Mooren ulcers; or the ulcer or ulcers are a symptom of ulcerative colitis.
- 5
120. A method of treating a condition in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient, wherein said condition
- 10 is an ocular condition, a cardiovascular condition, a cancer, Crow-Fukase (POEMS) syndrome, a diabetic condition, sickle cell anaemia, chronic inflammation, systemic lupus, glomerulonephritis, synovitis, inflammatory bowel disease, Crohn's disease, glomerulonephritis, rheumatoid arthritis, osteoarthritis, multiple sclerosis, graft rejection, Lyme disease, sepsis, von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease, polycystic
- 15 kidney disease, fibrosis, sarcoidosis, cirrhosis, thyroiditis, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma or edema following burns, trauma, radiation, stroke, hypoxia, ischemia, ovarian hyperstimulation syndrome, preeclampsia,
- 20 menometrorrhagia, endometriosis, or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapox virus, protozoa or toxoplasmosis.
121. The method of Claim 120 wherein the ocular condition is ocular or macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser treatment complications, conjunctivitis, Stargardt's disease, Eales disease, retinopathy or macular degeneration.
- 25
122. The method of Claim 120 wherein the cardiovascular condition is atherosclerosis, restenosis, ischemia/reperfusion injury, vascular occlusion or carotid obstructive disease.
- 30

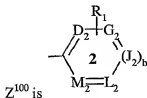
123. The method of Claim 120 wherein the cancer is a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy, Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma, leukemia or malignant ascites.
124. The method of Claim 120 wherein the diabetic condition is insulin-dependent diabetes mellitus glaucoma, diabetic retinopathy or microangiopathy.
125. A method of decreasing fertility in a patient, said method comprising the step of administering to the patient an effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolite thereof.
126. The method of Claim 116 wherein the compound or a physiologically acceptable salt, prodrug or biologically active metabolite thereof is administered in an amount effective to promote angiogenesis or vasculogenesis.
127. The method of Claim 114 wherein the protein kinase is Tie-2.
128. The method of Claim 126 wherein the compound of Formula I, or physiologically acceptable salt, prodrug or biologically active metabolite thereof, is administered in combination with a pro-angiogenic growth factor.
129. The method of Claim 128 wherein the pro-angiogenic growth factor is selected from the group consisting of VEGF, VEGF-B, VEGF-C, VEGF-D, VEGF-E, HGF, FGF-1, FGF-2, derivatives thereof and antiidotypic antibodies.
130. The method of Claim 126 wherein the patient is suffering from anemia, ischemia, infarct, transplant rejection, a wound, gangrene or necrosis.

131. The method of Claim 113 wherein the protein kinase activity is involved in T cell activation, B cell activation, mast cell degranulation, monocyte activation, the potentiation of an inflammatory response or a combination thereof.

132. A method of preparing a 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl intermediate represented by the following structural formula:

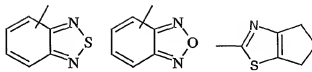


wherein:



or a group optionally substituted with R<sub>1</sub> selected

from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxaliny, quinazoliny, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,



benzothiazolyl,

, thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl,  
isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl,  
pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl,  
isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl,  
imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-  
dioxobenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-  
oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

$R_4$  and  $R_1$  represent one or more substituents for each occurrence

independently selected from the group consisting of hydrogen,  
halogen, -CN, -NO<sub>2</sub>, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-  
aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl,  
substituted or unsubstituted carboxamido, tetrazolyl,  
trifluoromethylcarbonylamino, trifluoromethylsulfonamido,  
substituted or unsubstituted alkyl, substituted or unsubstituted  
cycloalkyl, substituted or unsubstituted alkoxy, substituted or  
unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted  
or unsubstituted alkenyl, substituted or unsubstituted aryloxy,  
substituted or unsubstituted heteroaryloxy, substituted or  
unsubstituted heteroarylalkoxy, substituted or unsubstituted  
arylalkoxy, substituted or unsubstituted alkyl-S(O)<sub>p</sub>-, substituted or  
unsubstituted alkyl-S-, substituted or unsubstituted aryl-S(O)<sub>p</sub>-,  
substituted or unsubstituted heteroaryl-S(O)<sub>p</sub>-, substituted or  
unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl,  
substituted or unsubstituted cycloalkylalkyl, substituted or  
unsubstituted alkynyl, substituted or unsubstituted amino, substituted  
or unsubstituted aminoalkyl, substituted or unsubstituted amido  
groups, substituted or unsubstituted heteroarylthio, substituted or  
unsubstituted arylthio, -Z<sup>105</sup>-C(O)N(R)<sub>2</sub>, -Z<sup>105</sup>-N(R)-C(O)-Z<sup>200</sup>, -Z<sup>105</sup>-  
N(R)-S(O)<sub>2</sub>-Z<sup>200</sup>, -Z<sup>105</sup>-N(R)-C(O)-N(R)-Z<sup>200</sup>, R<sub>c</sub> and CH<sub>2</sub>OR<sub>c</sub>;

where  $R_e$  for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl,  $-\text{CH}_2-\text{NR}_d\text{R}_e$ ,  $-\text{W}-(\text{CH}_2)_t-\text{NR}_d\text{R}_e$ ,  $-\text{W}-(\text{CH}_2)_t-\text{O}-\text{alkyl}$ ,  $-\text{W}-(\text{CH}_2)_t-\text{S}-\text{alkyl}$ , or  $-\text{W}-(\text{CH}_2)_t-\text{OH}$ ;

5  $Z^{105}$  for each occurrence is independently a covalent bond or  $(\text{C}_1-\text{C}_6)$ ;

$Z^{200}$  for each occurrence is independently a substituted or unsubstituted  $(\text{C}_1-\text{C}_6)$ , substituted or unsubstituted phenyl or substituted or unsubstituted  $-(\text{C}_1-\text{C}_6)\text{-phenyl}$ ;

10  $R_d$  and  $R_e$  for each occurrence are independently H, alkyl, alkanoyl or  $\text{SO}_2\text{-alkyl}$ ; or  $R_d$ ,  $R_e$  and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

$t$  for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S,  $\text{S}(\text{O})$ ,  $\text{S}(\text{O})_2$ , or  $\text{NR}_f$ , wherein  $R_f$  for each occurrence is independently H or alkyl; or

15  $R_1$  is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2; and

R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

p is 1 or 2; and

20 b is 1 and  $D_2$ ,  $G_2$ ,  $J_2$ ,  $L_2$  and  $M_2$  are each independently selected from the group consisting of  $\text{CR}_a$  and N, provided that at least two of  $D_2$ ,  $G_2$ ,  $J_2$ ,  $L_2$  and  $M_2$  are  $\text{CR}_a$ ; or

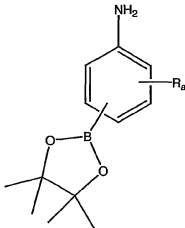
b is 0, and one of  $D_2$ ,  $G_2$ ,  $L_2$  and  $M_2$  is  $\text{NR}_a$ , one of  $D_2$ ,  $G_2$ ,  $L_2$  and  $M_2$  is  $\text{CR}_a$  and the remainder are independently selected from the group consisting of  $\text{CR}_a$  and N, wherein  $R_a$  is as defined above;

25 comprising the step of reacting in the presence of an aprotic base an acid chloride represented by the following structural formula:



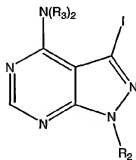
-861-

with a (4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl)aniline represented by the following structural formula:



to form said 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl intermediate.

133. The method of Claim 132, further comprising the step of reacting the 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl intermediate in the presence of tetrakis(triphenylphosphine)palladium(0) and sodium carbonate with a 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidine represented by the following structural formula:



wherein:

- $R_2$  is H or a group of the formula  $-Z^{101}-Z^{102}$ ,  
 $Z^{101}$  is a covalent bond,  $-(C_1-C_6)-$ ,  $-(C_1-C_6)-O-$ ,  $-(C_1-C_6)-C(O)-$ ,  $-(C_1-C_6)-C(O)O-$ ,  $-(C_1-C_6)-C(O)-NH-$ ,  $-(C_1-C_6)-C(O)-N((C_1-C_6))-$  or a substituted or unsubstituted phenyl group;

$Z^{102}$  is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted ( $C_1-C_6$ ), substituted or unsubstituted aryl, substituted or unsubstituted  $-C(O)$ -alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted  $-N(R)-(C_1-C_6)-OR$ , substituted or unsubstituted  $-N((C_1-C_6)-OR)_2$ , substituted or unsubstituted  $-N(R)-(C_1-C_6)-C(O)_2R$ , substituted or unsubstituted  $-(C_1-C_6)-N(R)-(C_1-C_6)-OR$ , substituted or unsubstituted  $-(C_1-C_6)-N(R)-(C_1-C_6)-N(R)_2$ , substituted or unsubstituted  $-(C_1-C_6)-C(O)N(R)-(C_1-C_6)-N(R)_2$ , substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted  $-N(R)-(C_1-C_6)-OR$ , oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  $-C(O)N(R)_2$ , substituted or unsubstituted  $-C(O)-(C_1-C_6)-N(R)_2$ ,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

$R_2$  is a group of the formula  $-B-E$ , wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted

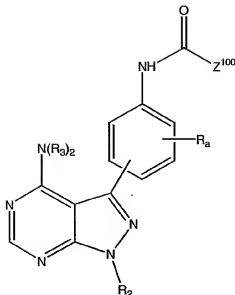
aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted aryl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted alkyl-N(R)-(C<sub>1</sub>-C<sub>6</sub>)-, substituted or unsubstituted heteroaryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted aryl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted alkyl-(C<sub>1</sub>-C<sub>6</sub>)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl; and

R<sub>3</sub> for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted -C(O)-heteroaryl or substituted or unsubstituted alkoxy;

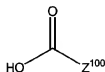
to form a compound represented by the following structural formula:



-864-

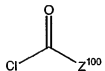


134. The method of Claim 133, further comprising the step of reacting a carboxylic acid represented by the following structural formula:



5

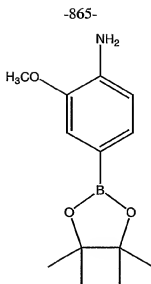
with oxalyl chloride and an aprotic base to form an acid chloride represented by the following structural formula:



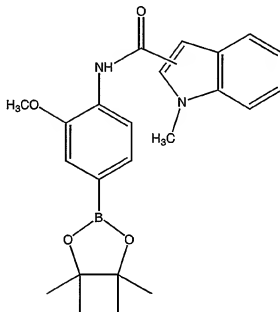
10

135. The method of Claim 132, 133 or 134 wherein  $Z^{100}$  is an indolyl which is optionally substituted with  $R_1$ .
136. The method of Claim 135, wherein  $Z^{100}$  is 1-methyl-indol-2-yl or 1-methyl-indol-3-yl.
137. The method of Claim 136, wherein the (4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl)aniline is represented by the following structural formula:

15



and the 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl intermediate is represented by the following structural formula:



5

138. The method of Claim 137, wherein R<sub>2</sub> is 4-(4-methylpiperazino)cyclohexyl.

10

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/09104

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/519; C07D 487/04

US CL : 544/262; 514/258.1

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/262; 514/258.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE, EAST

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94/18215 A1 (GENSIA, INC.) 18 August 1994 (18.08.1994), page 7 of the specification or see claim 43.	1-138
A	US 5,646,128 A (FIRESTEIN ET AL) 8 July 1997 (08.07.1997), see column 18, lines 5-23.	1-138

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

## Special categories of cited documents:

\* "A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z"

document member of the same patent family

Date of the actual completion of the international search

22 August 2002 (22.08.2002)

Date of mailing of the international search report

18 SEP 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks

Box PCT

Washington, D.C. 20531

Facsimile No. (703)305-3230

Authorized officer

Makum Shah

Telephone No. 703-306-1235

Form PCT/ISA/210 (second sheet) (July 1998)